

Single Nucleotide Polymorphisms sensitively predicting Adverse Drug Reactions (ADR) and Drug Efficacy

Technical Field

This invention relates to genetic polymorphisms useful for assessing cardiovascular risks in humans, including, but not limited to, atherosclerosis, ischemia/reperfusion, hypertension, restenosis, arterial inflammation, myocardial infarction, and stroke. In addition it relates to genetic polymorphisms useful for assessing the response to lipid lowering drug therapy. Specifically, the present invention identifies and describes gene variations which are individually present in humans with cardiovascular disease states, relate to humans with normal, or non-cardiovascular disease states, and/or in response to medications relevant to cardiovascular disease. Further, the present invention provides methods for the identification and therapeutic use of compounds as treatments of cardiovascular disease. Moreover, the present invention provides methods for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of cardiovascular disease, and for monitoring the efficacy of compounds in clinical trials. Still further, the present invention provides methods to use gene variations to predict personal medication schemes omitting adverse drug reactions and allowing an adjustment of the drug dose to achieve maximum benefit for the patient. Additionally, the present invention describes methods for the diagnostic evaluation and prognosis of various cardiovascular diseases, and for the identification of subjects exhibiting a predisposition to such conditions.

Background of the Invention

Cardiovascular disease is a major health risk throughout the industrialized world.

Cardiovascular diseases include but are not limited by the following disorders of the heart and the vascular system: congestive heart failure, myocardial infarction, atherosclerosis, ischemic diseases of the heart, coronary heart disease, all kinds of

atrial and ventricular arrhythmias, hypertensive vascular diseases and peripheral vascular diseases.

5 Heart failure is defined as a pathophysiologic state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirement of the metabolizing tissue. It includes all forms of pumping failure such as high-output and low-output, acute and chronic, right-sided or left-sided, systolic or diastolic, independent of the underlying cause.

10 Myocardial infarction (MI) is generally caused by an abrupt decrease in coronary blood flow that follows a thrombotic occlusion of a coronary artery previously narrowed by arteriosclerosis. MI prophylaxis (primary and secondary prevention) is included as well as the acute treatment of MI and the prevention of complications.

15 Ischemic diseases are conditions in which the coronary flow is restricted resulting in an perfusion which is inadequate to meet the myocardial requirement for oxygen. This group of diseases include stable angina, unstable angina and asymptomatic ischemia.

20 Arrhythmias include all forms of atrial and ventricular tachyarrhythmias (atrial tachycardia, atrial flutter, atrial fibrillation, atrio-ventricular reentrant tachycardia, preexcitation syndrome, ventricular tachycardia, ventricular flutter, ventricular fibrillation) as well as bradycardic forms of arrhythmias.

25 Hypertensive vascular diseases include primary as well as all kinds of secondary arterial hypertension (renal, endocrine, neurogenic, others).

30 Peripheral vascular diseases are defined as vascular diseases in which arterial and/or venous flow is reduced resulting in an imbalance between blood supply and tissue oxygen demand. It includes chronic peripheral arterial occlusive disease (PAOD),

acute arterial thrombosis and embolism, inflammatory vascular disorders, Raynaud's phenomenon and venous disorders.

Atherosclerosis, the most prevalent of vascular diseases, is the principal cause of heart attack, stroke, and gangrene of the extremities, and thereby the principal cause of death. Atherosclerosis is a complex disease involving many cell types and molecular factors (for a detailed review, see Ross, 1993, Nature 362: 801-809 and Lusis, A. J., Nature 407, 233-241 (2000)). The process, in normal circumstances a protective response to insults to the endothelium and smooth muscle cells (SMCs) of the wall of the artery, consists of the formation of fibrofatty and fibrous lesions or plaques, preceded and accompanied by inflammation. The advanced lesions of atherosclerosis may occlude the artery concerned, and result from an excessive inflammatory-fibroproliferative response to numerous different forms of insult. For example, shear stresses are thought to be responsible for the frequent occurrence of atherosclerotic plaques in regions of the circulatory system where turbulent blood flow occurs, such as branch points and irregular structures.

The first observable event in the formation of an atherosclerotic plaque occurs when blood-borne monocytes adhere to the vascular endothelial layer and transmigrate through to the sub-endothelial space. Adjacent endothelial cells at the same time produce oxidized low density lipoprotein (LDL). These oxidized LDLs are then taken up in large amounts by the monocytes through scavenger receptors expressed on their surfaces. In contrast to the regulated pathway by which native LDL (nLDL) is taken up by nLDL specific receptors, the scavenger pathway of uptake is not regulated by the monocytes.

These lipid-filled monocytes are called foam cells, and are the major constituent of the fatty streak. Interactions between foam cells and the endothelial and SMCs which surround them lead to a state of chronic local inflammation which can eventually lead to smooth muscle cell proliferation and migration, and the formation of a fibrous

plaque. Such plaques occlude the blood vessel concerned and thus restrict the flow of blood, resulting in ischemia.

Ischemia is a condition characterized by a lack of oxygen supply in tissues of organs due to inadequate perfusion. Such inadequate perfusion can have number of natural causes, including atherosclerotic or restenotic lesions, anemia, or stroke, to name a few. Many medical interventions, such as the interruption of the flow of blood during bypass surgery, for example, also lead to ischemia. In addition to sometimes being caused by diseased cardiovascular tissue, ischemia may sometimes affect cardiovascular tissue, such as in ischemic heart disease. Ischemia may occur in any organ, however, that is suffering a lack of oxygen supply.

The most common cause of ischemia in the heart is atherosclerotic disease of epicardial coronary arteries. By reducing the lumen of these vessels, atherosclerosis causes an absolute decrease in myocardial perfusion in the basal state or limits appropriate increases in perfusion when the demand for flow is augmented. Coronary blood flow can also be limited by arterial thrombi, spasm, and, rarely, coronary emboli, as well as by ostial narrowing due to luetic aortitis. Congenital abnormalities, such as anomalous origin of the left anterior descending coronary artery from the pulmonary artery, may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults. Myocardial ischemia can also occur if myocardial oxygen demands are abnormally increased, as in severe ventricular hypertrophy due to hypertension or aortic stenosis. The latter can be present with angina that is indistinguishable from that caused by coronary atherosclerosis. A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxy-hemoglobin, is a rare cause of myocardial ischemia. Not infrequently, two or more causes of ischemia will coexist, such as an increase in oxygen demand due to left ventricular hypertrophy and a reduction in oxygen supply secondary to coronary atherosclerosis.

The foregoing studies are aimed at defining the role of particular gene variations presumed to be involved in the misleading of normal cellular function leading to cardiovascular disease. However, such approaches cannot identify the full panoply of gene variations that are involved in the disease process.

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At present, the only available treatments for cardiovascular disorders are pharmaceutical based medications that are not targeted to an individual's actual defect; examples include angiotensin converting enzyme (ACE) inhibitors and diuretics for hypertension, insulin supplementation for non-insulin dependent diabetes mellitus (NIDDM), cholesterol reduction strategies for dyslipidaemia, anticoagulants, β blockers for cardiovascular disorders and weight reduction strategies for obesity. If targeted treatment strategies were available it might be possible to predict the response to a particular regime of therapy and could markedly increase the effectiveness of such treatment. Although targeted therapy requires accurate diagnostic tests for disease susceptibility, once these tests are developed the opportunity to utilize targeted therapy will become widespread. Such diagnostic tests could initially serve to identify individuals at most risk of hypertension and could allow them to make changes in lifestyle or diet that would serve as preventative measures. The benefits associated by coupling the diagnostic tests with a system of targeted therapy could include the reduction in dosage of administered drugs and thus the amount of unpleasant side effects suffered by an individual. In more severe cases a diagnostic test may suggest that earlier surgical intervention would be useful in preventing a further deterioration in condition.

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It is an object of the invention to provide genetic diagnosis of predisposition or susceptibility for cardiovascular diseases. Another related object is to provide treatment to reduce or prevent or delay the onset of disease in those predisposed or susceptible to this disease. A further object is to provide means for carrying out this diagnosis.

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Accordingly, a first aspect of the invention provides a method of diagnosis of disease in an individual, said method comprising determining one, various or all genotypes in said individual of the genes listed in the Examples.

5 In another aspect, the invention provides a method of identifying an individual predisposed or susceptible to a disease, said method comprising determining one, various or all genotypes in said individual of the genes listed in the Examples.

10 The invention is of advantage in that it enables diagnosis of a disease or of certain disease states via genetic analysis which can yield useable results before onset of disease symptoms, or before onset of severe symptoms. The invention is further of advantage in that it enables diagnosis of predisposition or susceptibility to a disease or of certain disease states via genetic analysis.

15 The invention may also be of use in confirming or corroborating the results of other diagnostic methods. The diagnosis of the invention may thus suitably be used either as an isolated technique or in combination with other methods and apparatus for diagnosis, in which latter case the invention provides a further test on which a diagnosis may be assessed.

20 The present invention stems from using allelic association as a method for genotyping individuals; allowing the investigation of the molecular genetic basis for cardiovascular diseases. In a specific embodiment the invention tests for the polymorphisms in the sequences of the listed genes in the Examples. The invention demonstrates a link between this polymorphisms and predispositions to cardiovascular diseases by showing that allele frequencies significantly differ when individuals with "bad" serum lipids are compared to individuals with "good" serum levels. The meaning of "good and bad" serum lipid levels is defined in Table 1a.

30 The PROCAM algorithm defines also a risk assessment based on lipids (LDL-cholesterol, HDL-cholesterol, triglycerides) and risk factors like smoking, high blood

pressure or diabetes mellitus (Assmann, G., Schulte, H. von Eckardstein, A: Am J Cardiol 77 (1996): 1179-1184).

Certain disease states would benefit, that is to say the suffering of the patient may be reduced or prevented or delayed, by administration of treatment or therapy in advance of disease appearance; this can be more reliably carried out if advance diagnosis of predisposition or susceptibility to disease can be diagnosed.

Pharmacogenomics and adverse drug reactions

Adverse drug reactions (ADRs) remain a major clinical problem. A recent meta-analysis suggested that in the USA in 1994, ADRs were responsible for 100 000 deaths, making them between the fourth and sixth commonest cause of death (Lazarou 1998, J. Am. Med. Assoc. 279:1200). Although these figures have been heavily criticized, they emphasize the importance of ADRs. Indeed, there is good evidence that ADRs account for 5% of all hospital admissions and increase the length of stay in hospital by two days at an increased cost of ~\$2500 per patient. ADRs are also one of the commonest causes of drug withdrawal, which has enormous financial implications for the pharmaceutical industry. ADRs, perhaps fortunately, only affect a minority of those taking a particular drug. Although factors that determine susceptibility are unclear in most cases, there is increasing interest in the role of genetic factors. Indeed, the role of inheritable variations in predisposing patients to ADRs has been appreciated since the late 1950s and early 1960s through the discovery of deficiencies in enzymes such as pseudocholinesterase (butyrylcholinesterase) and glucose-6-phosphate dehydrogenase (G6PD). More recently, with the first draft of the human genome just completed, there has been renewed interest in this area with the introduction of terms such as pharmacogenomics and toxicogenomics. Essentially, the aim of pharmacogenomics is to produce personalized medicines, whereby administration of the drug class and dosage is tailored to an individual genotype. Thus, the term pharmacogenomics embraces both efficacy and toxicity.

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") specifically inhibit the enzyme HMG-CoA reductase which catalyzes the rate limiting step in cholesterol biosynthesis. These drugs are effective in reducing the primary and secondary risk of coronary artery disease and coronary events, such as heart attack, in middle-aged and older men and women, in both diabetic and non-diabetic patients, and are often prescribed for patients with hyperlipidemia. Statins used in secondary prevention of coronary artery or heart disease significantly reduce the risk of stroke, total mortality and morbidity and attacks of myocardial ischemia; the use of statins is also associated with improvements in endothelial and fibrinolytic functions and decreased platelet thrombus formation.

The tolerability of these drugs during long term administration is an important issue. Adverse reactions involving skeletal muscle are not uncommon, and sometimes serious adverse reactions involving skeletal muscle such as myopathy and rhabdomyolysis may occur, requiring discontinuation of the drug. In addition an increase in serum creatine kinase (CK) may be a sign of a statin related adverse event. The extend of such adverse events can be read from the extend of the CK level increase (as compared to the upper limit of normal [ULN]).

Occasionally arthralgia, alone or in association with myalgia, has been reported. Also an elevation of liver transaminases has been associated with statin administration.

It was shown that the drug response to statin therapy is a class effects, i.e. all known and presumably also all so far undiscovered statins share the same beneficial and harmful effects (Ucar, M. et al., Drug Safety 2000, 22:441). It follows that the discovery of diagnostic tools to predict the drug response to a single statin will also be of aid to guide therapy with other statins.

The present invention provides diagnostic tests to predict the patient's individual response to statin therapy. Such responses include, but are not limited by the extent

of adverse drug reactions, the level of lipid lowering or the drug's influence on disease states. Those diagnostic tests may predict the response to statin therapy either alone or in combination with another diagnostic test or another drug regimen.

5 **Detailed Description of the Invention**

The present invention is based at least in part on the discovery that a specific allele of a polymorphic region of a so called "candidate gene" (as defined below) is associated with CVD or drug response.

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For the present invention the following candidate genes were analyzed:

- Genes found to be expressed in cardiac tissue (Hwang et al., Circulation 1997, 96:4146-4203).
- 15 - Genes from the following metabolic pathways and their regulatory elements:

Lipid metabolism

Numerous studies have shown a connection between serum lipid levels and cardiovascular diseases. Candidate genes falling into this group include but are not limited by genes of the cholesterol pathway, apolipoproteins and their modifying factors.

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Coagulation

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Ischemic diseases of the heart and in particular myocardial infarction may be caused by a thrombotic occlusion. Genes falling into this group include all genes of the coagulation cascade and their regulatory elements.

Inflammation

Complications of atherosclerosis are the most common causes of death in Western societies. In broad outline atherosclerosis can be considered to be a form of chronic inflammation resulting from interaction modified lipoproteins, monocyte-derived macrophages, T cells, and the normal cellular elements of the arterial wall. This inflammatory process can ultimately lead to the development of complex lesions, or plaques, that protrude into the arterial lumen. Finally plaque rupture and thrombosis result in the acute clinical complications of myocardial infarction and stroke (Glass et al., Cell 2001, 104:503-516).

It follows that all genes related to inflammatory processes, including but not limited by cytokines, cytokine receptors and cell adhesion molecules are candidate genes for CVD.

Glucose and energy metabolism

As glucose and energy metabolism is interdependent with the metabolism of lipids (see above) also the former pathways contain candidate genes. Energy metabolism in general also relates to obesity, which is an independent risk factor for CVD (Melanson et al., Cardiol Rev 2001 9:202-207). In addition high blood glucose levels are associated with many microvascular and macrovascular complications and may therefore affect an individuals disposition to CVD (Duckworth, Curr Atheroscler Rep 2001, 3:383-391).

Hypertension

As hypertension is an independent risk factor for CVD, also genes that are involved in the regulation of systolic and diastolic blood pressure affect an individuals risk for CVD (Safar, Curr Opin Cardiol 2000, 15:258-263). Interestingly hypertension and diabetes (see above) appear to be interdependent, since hypertension is

approximately twice as frequent in patients with diabetes compared with patients without the disease. Conversely, recent data suggest that hypertensive persons are more predisposed to the development of diabetes than are normotensive persons (Sowers et al., Hypertension 2001, 37:1053-1059).

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Genes related to drug response

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Those genes include metabolic pathways involved in the absorption, distribution, metabolism, excretion and toxicity (ADMET) of drugs. Prominent members of this group are the cytochrome P450 proteins which catalyze many reactions involved in drug metabolism.

Unclassified genes

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As stated above, the mechanisms that lead to cardiovascular diseases or define the patient's individual response to drugs are not completely elucidated. Hence also candidate genes were analysed, which could not be assigned to the above listed categories. The present invention is based at least in part on the discovery of polymorphisms, that lie in genomic regions of unknown physiological function.

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Results

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After conducting an association study, we surprisingly found polymorphic sites in a number of candidate genes which show a strong correlation with the following phenotypes of the patients analysed: "Healthy" as used herein refers to individuals that neither suffer from existing CVD, nor exhibit an increased risk for CVD through their serum lipid level profile. "CVD prone" as used herein refers to individuals with existing CVD and/or a serum lipid profile that confers a high risk to get CVD (see Table 1a for definitions of healthy and CVD prone serum lipid levels). "High responder" as used herein refers to patients who benefit from relatively small amounts of a given drug. "Low responder" as used herein refers to patients who need

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relatively high doses in order to obtain benefit from the medication. "Tolerant patient" refers to individuals who can tolerate high doses of a medicament without exhibiting adverse drug reactions. "ADR patient" as used herein refers to individuals who suffer from ADR or show clinical symptoms (like creatine kinase elevation in blood) even after receiving only minor doses of a medicament (see Table 1b for a detailed definition of drug response phenotypes).

Polymorphic sites in candidate genes that were found to be significantly associated with either of the above mentioned phenotypes will be referred to as "phenotype associated SNPs" (PA SNPs). The respective genomic loci that harbour PA SNPs will be referred to as "phenotype associated genes" (PA genes), irrespective of the actual function of this gene locus.

In particular we surprisingly found PA SNPs associated with CVD, drug efficacy (EFF) or adverse drug reactions (ADR) in the following genes.

ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11

The membrane-associated protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intra-cellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the MDR/TAP subfamily. Members of the MDR/TAP subfamily are involved in multidrug resistance. The protein encoded by this gene is the major canalicular bile salt export pump in man. Mutations in this gene cause a form of progressive familial intrahepatic cholestases which are a group of inherited disorders with severe cholestatic liver disease from early infancy.

ABCB4: ATP-binding cassette, sub-family B (MDR/TAP), member 4

The membrane-associated protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intra-cellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the MDR/TAP subfamily. Members of the MDR/TAP subfamily are involved in multidrug resistance as well as antigen presentation. This gene encodes a full transporter and member of the p-glycoprotein family of membrane proteins with phosphatidylcholine as its substrate. The function of this protein has not yet been determined; however, it may involve transport of phospholipids from liver hepatocytes into bile. Alternative splicing of this gene results in several products of undetermined function.

ABCC1: ATP-binding cassette, sub-family C (CFTR/MRP), member 1

The protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intra-cellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). This full transporter is a member of the MRP subfamily which is involved in multi-drug resistance. This protein functions as a multispecific organic anion transporter, with oxidized glutathione, cysteinyl leukotrienes, and activated aflatoxin B1 as substrates. This protein also transports glucuronides and sulfate conjugates of steroid hormones and bile salts. Alternative splicing by exon deletion results in several splice variants but maintains the original open reading frame in all forms.

ACTB mRNA for mutant beta-actin

Beta actin is one of six different actin isoforms which have been identified. ACTB is one of the two nonmuscle cytoskeletal actins. Actins are highly conserved proteins

that are involved in cell motility, structure and integrity. Alpha actins are a major constituent of the contractile apparatus.

ACTIN, ALPHA SKELETAL MUSCLE (ALPHA-ACTIN 1)

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Actin alpha 1 which is expressed in skeletal muscle is one of six different actin isoforms which have been identified. Actins are highly conserved proteins that are involved in cell motility, structure and integrity. Alpha actins are a major constituent of the contractile apparatus.

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ADCYAP1: adenylate cyclase activating polypeptide 1 (pituitary)

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This gene encodes adenylate cyclase activating polypeptide 1. Mediated by adenylate cyclase activating polypeptide 1 receptors, this polypeptide stimulates adenylate cyclase and subsequently increases the cAMP level in target cells. Adenylate cyclase activating polypeptide 1 is not only a hypophysiotropic hormone, but also functions as a neurotransmitter and neuromodulator. In addition, it plays a role in paracrine and autocrine regulation of certain types of cells. This gene is composed of five exons. Exons 1 and 2 encode the 5' UTR and signal peptide, respectively; exon 4 encodes an adenylate cyclase activating polypeptide 1-related peptide; and exon 5 encodes the mature peptide and 3' UTR. This gene encodes three different mature peptides, including two isotypes: a shorter form and a longer form.

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ADRB3: adrenergic, beta-3-, receptor

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The ADRB3 gene product, beta-3-adrenergic receptor, is located mainly in adipose tissue and is involved in the regulation of lipolysis and thermogenesis. Beta adrenergic receptors are involved in the epinephrine and norepinephrine-induced activation of adenylate cyclase through the action of G proteins.

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AGL: amylo-1, 6-glucosidase, 4-alpha-glucanotransferase (glycogen debranching enzyme, glycogen storage disease type III)

Glycogen debranching enzyme is involved in glycogen degradation and has two independent catalytic activities: a 4-alpha-glucotransferase activity (EC 2.4.1.25) and a amylo-1,6-glucosidase activity (EC 3.4.1.33). Both activities occur at different sites on the single polypeptide chain. Mutations in this gene cause glycogen storage disease. A wide range of clinical and enzymatic variability occurs in glycogen debrancher deficiency, some of which may be due to tissue-specific alternative splicing. Six splice variants that differ in the 5' end have been identified in liver and muscle tissue. Variants 1, 5, and 6 are present in both liver and muscle, whereas variants 2, 3, and 4 occur in muscle. Variants 1 through 4 encode identical proteins (isoform 1) that include 27 N-terminal amino acids not found in splice variants 5 and 6. Variants 5 and 6 encode different amino-terminal ends of 10 and 11 amino acids in protein isoforms 2 and 3, respectively, with the remainder of the peptide identical to that of isoforms 1..

AKAP1: A kinase (PRKA) anchor protein 1

Anchors cAMP-dependent protein kinase near its physiological substrates, interacts with both the type I and type II regulatory subunits.

Angiotensinogen gene

The protein encoded by this gene, pre-angiotensinogen or angiotensinogen precursor, is expressed in the liver and is cleaved by the enzyme renin in response to lowered blood pressure. The resulting product, angiotensin I is then cleaved by angiotensin converting enzyme (ACE) to generate the physiologically active enzyme angiotensin II. The protein is involved in maintaining blood pressure and in the pathogenesis of essential hypertension and preeclampsia.

ANXA6: annexin A6

Annexin VI belongs to a family of calcium-dependent membrane and phospholipid binding proteins. Although their functions are still not clearly defined, several members of the annexin family have been implicated in membrane-related events along exocytotic and endocytotic pathways. The annexin VI gene is approximately 60 kbp long and contains 26 exons. It encodes a protein of about 68 kDa that consists of eight 68-amino acid repeats separated by linking sequences of variable lengths. It is highly similar to human annexins I and II sequences, each of which contain four such repeats. Exon 21 of annexin VI is alternatively spliced, giving rise to two isoforms that differ by a 6-amino acid insertion at the start of the seventh repeat. Annexin VI has been implicated in mediating the endosome aggregation and vesicle fusion in secreting epithelia during exocytosis.

AP2B1: adaptor-related protein complex 2, beta 1 subunit

The beta adaptin subunit is part of the clathrin coat assembly complex which links clathrin to receptors in coated pits and vesicles. These vesicles are involved in endocytosis and Golgi processing. The beta 1 subunit is one of the assembly proteins which binds to clathrin and initiates coat formation.

APOA1: apolipoprotein A-I

APOA1 promotes cholesterol efflux from tissues to the liver for excretion. Apolipoprotein A-I is the major protein component of high density lipoprotein (HDL) in the plasma. Synthesized in the liver and small intestine, it consists of two identical chains of 77 amino acids; an 18-amino acid signal peptide is removed co-translationally and a 6-amino acid propeptide is cleaved post-translationally. Variation in the latter step, in addition to modifications leading to so-called isoforms, is responsible for some of the polymorphism observed. APOA1 is a cofactor for lecithin cholesterolacyltransferase (LCAT) which is responsible for the formation of

most plasma cholesteryl esters. The APOA1, APOC3 and APOA4 genes are closely linked in both rat and human genomes. The A-I and A-IV genes are transcribed from the same strand, while the C-III gene is transcribed convergently in relation to A-I. Defects in the apolipoprotein A-I gene are associated with HDL deficiency and Tangier disease.

APOA4: apolipoprotein A-IV

Apolipoprotein (apo) A-IV gene contains 3 exons separated by two introns. A sequence polymorphism has been identified in the 3'UTR of the third exon. The primary translation product is a 396-residue preprotein which after proteolytic processing is secreted its primary site of synthesis, the intestine, in association with chylomicron particles. Although its precise function is not known, apo A-IV is a potent activator of lecithin-cholesterol acyltransferase in vitro.

APOB: apolipoprotein B

Apolipoprotein B (ApoB) is the main apolipoprotein of chylomicrons and low density lipoproteins (LDL). The protein occurs in the plasma in 2 main isoforms, apoB-48 and apoB-100. The first is synthesized exclusively by the gut, the second by the liver. The intestinal (B-48) and hepatic (B-100) forms of apoB are coded by a single gene and by a single mRNA transcript larger than 16 kb. The 2 proteins share a common amino terminal sequence. In the ApoB-100 isoform the precursor has 4,563 amino acids, and the mature apoB-100 has 4,536 amino acid residues. Mature, circulating B-48 is homologous over its entire length (estimated to be between 2,130 and 2,144 amino acid residues) with the amino-terminal portion of B-100 and contains no sequence from the carboxyl end of B-100. From structural studies, it is thought that apoB-48 represents the amino-terminal 47% of apoB-100 and that the carboxyl terminus of apoB-48 is in the vicinity of residue 2151 of apoB-100. Apolipoprotein B-48 may be the product of an intestinal mRNA with an in-frame UAA stop codon resulting from a C-to-U change in the codon CAA encoding

Gln(2153) in apoB-100 mRNA. Since only the sequence that codes B-100 is present in genomic DNA, this presents the possibility of an organ-specific introduction of a stop codon to an mRNA and the change from CAA to UAA of codon 2153 of the message as a unique RNA editing process..

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APOD: apolipoprotein D

Apolipoprotein D (Apo-D) is a component of high density lipoprotein that has no marked similarity to other apolipoprotein sequences. It has a high degree of
10 homology to plasma retinol-binding protein and other members of the alpha 2 microglobulin protein superfamily of carrier proteins, also known as lipocalins. It is a glycoprotein of estimated molecular weight 33 KDa. Apo-D is closely associated with the enzyme lecithin:cholesterol acyltransferase - an enzyme involved in lipoprotein metabolism.

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Apolipoprotein B

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APXL: apical protein-like (*Xenopus laevis*)

The protein encoded by this gene shares significant similarities with the apical protein from *Xenopus laevis* which is implicated in amiloride-sensitive sodium channel activity. This gene is a strong candidate gene for ocular albinism type 1 syndrome.

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ARF4: ADP-ribosylation factor 4

ADP-ribosylation factor 4 (ARF4) is a member of the human ARF gene family. These genes encode small guanine nucleotide-binding proteins that stimulate the ADP-ribosyltransferase activity of cholera toxin and play a role in vesicular trafficking and as activators of phospholipase D. The gene products include 6 ARF proteins and 11 ARF-like proteins and constitute 1 family of the RAS superfamily. The ARF proteins are categorized as class I (ARF1, ARF2, and ARF3), class II (ARF4 and ARF5) and class III (ARF6). The members of each class share a common gene organization. The ARF4 gene spans approximately 12kb and contains six exons and five introns. The ARF4 is the most divergent member of the human ARFs. Conflicting Map positions at 3p14 or 3p21 have been reported for this gene.

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ATP1A2: ATPase, Na⁺/K⁺ transporting, alpha 2 (+) polypeptide

Alpha 2 subunit of the sodium- and potassium-transporting ATPase; required for Na⁺ and K⁺ gradient maintenance across plasma membrane.

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ATP1B1: ATPase, Na⁺/K⁺ transporting, beta 1 polypeptide

Beta 1 subunit of Na⁺/K⁺-ATPase.

5 ATP1B3: ATPase, Na⁺/K⁺ transporting, beta 3 polypeptide

Beta 3 subunit of the Na⁺/K⁺ -ATPase.

10 ATP2A2: ATPase, Ca⁺⁺ transporting, cardiac muscle, slow twitch 2

Slow twitch cardiac muscle Ca²⁺-ATPase; pumps calcium, may have a role in calcium signaling pathways.

15 ATP5G1: ATP synthase, H⁺ transporting, mitochondrial F0 complex, subunit c (subunit 9), isoform 1

Isoform 1 (P1) of subunit c, H⁺-translocating subunit of F0 ATP synthase; catalyzes the synthesis of ATP during oxidative phosphorylation.

20 ATP6V1E: ATPase, H⁺ transporting, lysosomal 31kD, V1 subunit E

This gene encodes a component of vacuolar ATPase (V-ATPase), a multisubunit enzyme that mediates acidification of eukaryotic intracellular organelles. V-ATPase dependent organelle acidification is necessary for such intracellular processes as protein sorting, zymogen activation, and receptor-mediated endocytosis. V-ATPase is comprised of a cytosolic V1 domain and a transmembrane V0 domain. The V1 domain consists of a hexamer of three A and three B subunits plus the C, D, and E subunits. It contains the ATP catalytic site. The encoded protein is known as the E subunit and is found ubiquitously. Pseudogenes for this gene have been found in the genome.

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ATPase, Ca⁺⁺ transporting, cardiac muscle, fast twitch 1

Fast-twitch skeletal muscle sarcoplasmic reticulum Ca²⁺-ATPase; pumps calcium.

5 AXIN1: axin

Strongly similar to murine Axin; may regulate embryonic axis formation.

10 BMPR1A: bone morphogenetic protein receptor, type IA

The bone morphogenetic protein (BMP) receptors are a family of transmembrane serine/threonine kinases that include the type I receptors BMPR1A and BMPR1B and the type II receptor BMPR2. These receptors are also closely related to the activin receptors, ACVR1 and ACVR2. The ligands of these receptors are members of the TGF-beta superfamily. TGF-betas and activins transduce their signals through the formation of heteromeric complexes with 2 different types of serine (threonine) kinase receptors: type I receptors of about 50-55 kD and type II receptors of about 70-80 kD. Type II receptors bind ligands in the absence of type I receptors, but they require their respective type I receptors for signaling, whereas type I receptors require their respective type II receptors for ligand binding.

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BRD3: bromodomain containing 3

This gene was identified based on its homology to the gene encoding the RING3 protein, a serine/threonine kinase. The gene localizes to 9q34, a region which contains several major histocompatibility complex (MHC) genes. The function of the encoded protein is not known.

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CACNA1C: calcium channel, voltage-dependent, L type, alpha 1C subunit

Alpha 1C subunit of the voltage-dependent calcium channel; channel is of the L type and is expressed in the heart.

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CALB2: calbindin 2, (29kD, calretinin)

Calbindin 2 (calretinin), closely related to calbindin 1, is an intracellular calcium-binding protein belonging to the troponin C superfamily. Calbindin 1 is known to be involved in the vitamin-D-dependent calcium absorption through intestinal and renal epithelia, while the function of neuronal calbindin 1 and calbindin 2 is poorly understood. The sequence of the calbindin 2 cDNA reveals an open reading frame of 271 codons coding for a protein of 31,520 Da, and shares 58% identical residues with human calbindin 1. Calbindin 2 contains five presumably active and one presumably inactive calcium-binding domains. Comparison with the partial sequences available for chick and guinea pig calbindin 2 reveals that the protein is highly conserved in evolution. The calbindin 2 message was detected in the brain, while absent from heart muscle, kidney, liver, lung, spleen, stomach and thyroid gland. There are two additional forms of alternatively spliced calbindin 2 mRNAs encoding C-terminally truncated proteins. Exon 7 can splice to exon 9, resulting in a frame shift and a translational stop at the second codon of exon 9, and encoding calretinin-20k. Exon 7 can also splice to exon 10, resulting in a frame shift and a translational stop at codon 15 of exon 10, and encoding calretinin-22k. The truncated proteins are able to bind calcium..

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25**CALCIUM-TRANSPORTING ATPASE PLASMA MEMBRANE, ISOFORMS 3A/3B (EC 3.6.1.38) (CALCIUM PUMP) (PMCA3)**

Plasma membrane Ca²⁺-ATPase 3; pumps calcium.

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CALM3: calmodulin 3 (phosphorylase kinase, delta)

Calmodulin 3; binds calcium.

5 CAV1: caveolin 1, caveolae protein, 22kD

The scaffolding protein encoded by this gene is the main component of the caveolae plasma membranes found in most cell types. The protein links integrin subunits to the tyrosine kinase FYN, an initiating step in coupling integrins to the Ras-ERK
10 pathway and promoting cell cycle progression. The gene is a tumor suppressor gene candidate and a negative regulator of the Ras-p42/44 MAP kinase cascade. CAV1 and CAV2 are located next to each other on chromosome 7 and express colocalizing proteins that form a stable hetero-oligomeric complex. By using alternative initiation codons in the same reading frame, two isoforms (alpha and beta) are encoded by a
15 single transcript from this gene.

CAV3: caveolin 3

This gene encodes a caveolin family member, which functions as a component of the caveolae plasma membranes found in most cell types. Caveolin proteins are proposed
20 to be scaffolding proteins for organizing and concentrating certain caveolin-interacting molecules. Mutations identified in this gene lead to interference with protein oligomerization or intra-cellular routing, disrupting caveolae formation and resulting in Limb-Girdle muscular dystrophy type-1C (LGMD-1C), hyperCKemia or
25 rippling muscle disease (RMD). Alternative splicing has been identified for this locus, with inclusion or exclusion of a differentially spliced intron. In addition, transcripts utilize multiple polyA sites and contain two potential translation initiation sites.

CCR2: chemokine (C-C motif) receptor 2

This gene encodes two isoforms of a receptor for monocyte chemoattractant protein-1, a chemokine which specifically mediates monocyte chemotaxis. Monocyte chemoattractant protein-1 is involved in monocyte infiltration in inflammatory diseases such as rheumatoid arthritis as well as in the inflammatory response against tumors. The receptors encoded by this gene mediate agonist-dependent calcium mobilization and inhibition of adenylyl cyclase. This gene is located in the chemokine receptor gene cluster region. Two alternatively spliced transcript variants are expressed by the gene.

CDH1: cadherin 1, type 1, E-cadherin (epithelial)

This gene is a classical cadherin from the cadherin superfamily. The encoded protein is a calcium dependent cell-cell adhesion glycoprotein comprised of five extracellular cadherin repeats, a transmembrane region and a highly conserved cytoplasmic tail. Mutations in this gene are correlated with gastric, breast, colorectal, thyroid and ovarian cancer. Loss of function is thought to contribute to progression in cancer by increasing proliferation, invasion, and/or metastasis. The ectodomain of this protein mediates bacterial adhesion to mammalian cells and the cytoplasmic domain is required for internalization. Identified transcript variants arise from mutation at consensus splice sites.

CDH11: cadherin 11, type 2, OB-cadherin (osteoblast)

This gene encodes a type II classical cadherin from the cadherin superfamily, integral membrane proteins that mediate calcium-dependent cell-cell adhesion. Mature cadherin proteins are composed of a large N-terminal extracellular domain, a single membrane-spanning domain, and a small, highly conserved C-terminal cytoplasmic domain. Type II (atypical) cadherins are defined based on their lack of a HAV cell adhesion recognition sequence specific to type I cadherins. Expression of this

particular cadherin in osteoblastic cell lines, and its upregulation during differentiation, suggests a specific function in bone development and maintenance. Two splice variants have been identified, one of which encodes an isoform with a truncated cytoplasmic domain.

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CDH13: cadherin 13, H-cadherin (heart)

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This gene is a member of the cadherin superfamily. The encoded protein is a calcium dependent cell-cell adhesion glycoprotein comprised of five extracellular cadherin repeats, a transmembrane region but, unlike the typical cadherin superfamily member, lacks the highly conserved cytoplasmic region. This particular cadherin is a putative mediator of cell-cell interaction in the heart and may act as a negative regulator of neural cell growth. The gene locus is hypermethylated or deleted in breast, ovarian and lung cancers. Two major mRNA transcripts encoding identical proteins are found, products of alternative polyadenylation sites.

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CENPC1: centromere protein C 1

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Centromere protein C 1 is a centromere autoantigen and a component of the inner kinetochore plate. The protein is required for maintaining proper kinetochore size and a timely transition to anaphase. A putative pseudogene exists on chromosome 12.

Cholesteryl ester transfer protein (CETP)

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Cholesteryl ester transfer protein (CETP) transfers cholesteryl esters between lipoproteins. CETP may effect susceptibility to atherosclerosis.

CLCN4: chloride channel 4

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The CLCN family of voltage-dependent chloride channel genes comprises nine members (CLCN1-7, Ka and Kb) which demonstrate quite diverse functional

characteristics while sharing significant sequence homology. Chloride channel 4 has an evolutionary conserved CpG island and is conserved in both mouse and hamster. This gene is mapped in close proximity to APXL (Apical protein *Xenopus laevis*-like) and OA1 (Ocular albinism type I), which are both located on the human X chromosome at band p22.3. The physiological role of chloride channel 4 remains unknown but may contribute to the pathogenesis of neuronal disorders.

CLCNKA: chloride channel Ka

Putative chloride channel; member of the CLC family of voltage-gated chloride channels.

COL6A3: collagen, type VI, alpha 3

This gene encodes the alpha 3 chain, one of the three alpha chains of type VI collagen, a beaded filament collagen found in most connective tissues. The alpha 3 chain of type VI collagen is much larger than the alpha 1 and 2 chains. This difference in size is largely due to an increase in the number of subdomains, similar to von Willebrand Factor type A domains, found in the amino terminal globular domain of all the alpha chains. These domains have been shown to bind extracellular matrix proteins, an interaction that explains the importance of this collagen in organizing matrix components. Mutations in the type VI collagen genes are associated with Bethlem myopathy. In addition to the full length transcript, four transcript variants have been identified that encode proteins with N-terminal globular domains of varying sizes.

COL7A1: collagen, type VII, alpha 1 (epidermolysis bullosa, dystrophic, dominant and recessive)

This gene encodes the alpha chain of type VII collagen. The type VII collagen fibril, composed of three identical alpha collagen chains, is restricted to the basement zone

beneath stratified squamous epithelia. It functions as an anchoring fibril between the external epithelia and the underlying stroma. Mutations in this gene are associated with all forms of dystrophic epidermolysis bullosa. In the absence of mutations, however, an acquired form of this disease can result from an autoimmune response made to type VII collagen.

COL9A3: collagen, type IX, alpha 3

This gene encodes one of the three alpha chains of type IX collagen, the major collagen component of hyaline cartilage. Type IX collagen, a heterotrimeric molecule, is usually found in tissues containing type II collagen, a fibrillar collagen. Mutations in this gene are associated with multiple epiphyseal dysplasia.

COMT: catechol-O-methyltransferase

Catechol-O-methyltransferase catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine. This O-methylation results in one of the major degradative pathways of the catecholamine transmitters. In addition to its role in the metabolism of endogenous substances, COMT is important in the metabolism of catechol drugs used in the treatment of hypertension, asthma, and Parkinson disease. COMT is found in two forms in tissues, a soluble form (S-COMT) and a membrane-bound form (MB-COMT). The differences between S-COMT and MB-COMT reside within the N-termini. The transcript variants are formed through the use of alternative translation initiation sites and promoters.

COX10: COX10 homolog, cytochrome c oxidase assembly protein, heme A: farnesyltransferase (yeast)

Cytochrome c oxidase (COX), the terminal component of the mitochondrial respiratory chain, catalyzes the electron transfer from reduced cytochrome c to

oxygen. This component is a heteromeric complex consisting of 3 catalytic subunits encoded by mitochondrial genes and multiple structural subunits encoded by nuclear genes. The mitochondrially-encoded subunits function in electron transfer, and the nuclear-encoded subunits may function in the regulation and assembly of the complex. This nuclear gene encodes heme A:farnesyltransferase, which is not a structural subunit but required for the expression of functional COX and functions in the maturation of the heme A prosthetic group of COX. This protein is predicted to contain 7-9 transmembrane domains localized in the mitochondrial inner membrane. A gene mutation, which results in the substitution of a lysine for an asparagine (N204K), is identified to be responsible for cytochrome c oxidase deficiency. In addition, this gene is disrupted in patients with CMT1A (Charcot-Marie-Tooth type 1A) duplication and with HNPP (hereditary neuropathy with liability to pressure palsies) deletion.

CPB2: carboxypeptidase B2 (plasma, carboxypeptidase U)

Carboxypeptidases are enzymes that hydrolyze C-terminal peptide bonds. The carboxypeptidase family includes metallo-, serine, and cysteine carboxypeptidases. According to their substrate specificity, these enzymes are referred to as carboxypeptidase A (cleaving aliphatic residues) or carboxypeptidase B (cleaving basic amino residues). The protein encoded by this gene is activated by trypsin and acts on carboxypeptidase B substrates. After thrombin activation, the mature protein downregulates fibrinolysis. Polymorphisms have been described for this gene and its promoter region. Available sequence data analyses indicate splice variants that encode different isoforms.

CPO: coproporphyrinogen oxidase (coproporphyrin, harderoporphyrin)

Coproporphyrinogen; catalyzes oxidative decarboxylation in sixth step of heme biosynthesis.

CRYAB: crystallin, alpha B

Crystallins are separated into two classes: taxon-specific, or enzyme, and ubiquitous. The latter class constitutes the major proteins of vertebrate eye lens and maintains the transparency and refractive index of the lens. Since lens central fiber cells lose their nuclei during development, these crystallins are made and then retained throughout life, making them extremely stable proteins. Mammalian lens crystallins are divided into alpha, beta, and gamma families; beta and gamma crystallins are also considered as a superfamily. Alpha and beta families are further divided into acidic and basic groups. Seven protein regions exist in crystallins: four homologous motifs, a connecting peptide, and N- and C-terminal extensions. Alpha crystallins are composed of two gene products: alpha-A and alpha-B, for acidic and basic, respectively. Alpha crystallins can be induced by heat shock and are members of the small heat shock protein (sHSP also known as the HSP20) family. They act as molecular chaperones although they do not renature proteins and release them in the fashion of a true chaperone; instead they hold them in large soluble aggregates. Post-translational modifications decrease the ability to chaperone. These heterogeneous aggregates consist of 30-40 subunits; the alpha-A and alpha-B subunits have a 3:1 ratio, respectively. Two additional functions of alpha crystallins are an autokinase activity and participation in the intracellular architecture. Alpha-A and alpha-B gene products are differentially expressed; alpha-A is preferentially restricted to the lens and alpha-B is expressed widely in many tissues and organs. Elevated expression of alpha-B crystallin occurs in many neurological diseases; a missense mutation cosegregated in a family with a desmin-related myopathy.

CSF2RB: colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)

CSF2RB is a common beta chain of the high affinity receptor for IL-3, IL-5 and CSF. Defective CSF2RB has been reported to be associated with protein alveolar proteinosis.

CUBN: cubilin (intrinsic factor-cobalamin receptor)

5 Cubilin (CUBN) acts as a receptor for intrinsic factor-vitamin B12 complexes. The role of receptor is supported by the presence of 27 CUB domains. Cubilin is located within the epithelium of intestine and kidney. Mutations in CUBN may play a role in autosomal recessive megaloblastic anemia.

CXorf6: chromosome X open reading frame 6

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CYP17: cytochrome P450, subfamily XVII (steroid 17-alpha-hydroxylase), adrenal hyperplasia

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This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This protein localizes to the endoplasmic reticulum. It has both 17alpha-hydroxylase and 17,20-lyase activities and is a key enzyme in the steroidogenic pathway that produces progestins, mineralocorticoids, glucocorticoids, androgens, and estrogens. Mutations in this gene are associated with isolated steroid-17 alpha-hydroxylase deficiency, 17-alpha-hydroxylase/17,20-lyase deficiency, pseudohermaphroditism, and adrenal hyperplasia.

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CYP2C8: cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase), polypeptide 8

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This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This protein localizes to the endoplasmic reticulum and its expression is induced by phenobarbital. The enzyme is known to metabolize many xenobiotics, including the

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anticonvulsive drug mephenytoin, benzo(a)pyrene, 7-ethoxycoumarin, and the anti-cancer drug taxol. Two transcript variants for this gene have been described; it is thought that the longer form does not encode an active cytochrome P450 since its protein product lacks the heme binding site. This gene is located within a cluster of cytochrome P450 genes on chromosome 10q24.

CYP2E: cytochrome P450, subfamily IIE (ethanol-inducible)

This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This protein localizes to the endoplasmic reticulum and is induced by ethanol, the diabetic state, and starvation. The enzyme metabolizes both endogenous substrates, such as ethanol, acetone, and acetal, as well as exogenous substrates including benzene, carbon tetrachloride, ethylene glycol, and nitrosamines which are premutagens found in cigarette smoke. Due to its many substrates, this enzyme may be involved in such varied processes as gluconeogenesis, hepatic cirrhosis, diabetes, and cancer.

CYP3A4

This gene, CYP3A4, encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This protein localizes to the endoplasmic reticulum and its expression is induced by glucocorticoids and some pharmacological agents. This enzyme is involved in the metabolism of approximately half the drugs which are used today, including acetaminophen, codeine, cyclosporin A, diazepam and erythromycin. The enzyme also metabolizes some steroids and carcinogens. This gene is part of a cluster of cytochrome P450 genes on chromosome 7q21.1. Previously another CYP3A gene,

CYP3A3, was thought to exist; however, it is now thought that this sequence represents a transcript variant of CYP3A4.

CYP4F8: cytochrome P450, subfamily IVF, polypeptide 8

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This gene, CYP4F8, encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This protein localizes to the endoplasmic reticulum and functions as a 19-hydroxylase of prostaglandins in seminal vesicles. This gene is part of a cluster of cytochrome P450 genes on chromosome 19. Another member of this family, CYP4F3, is approximately 18 kb away.

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CYP8B1: cytochrome P450, subfamily VIII B (sterol 12- α -hydroxylase), polypeptide 1

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This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This endoplasmic reticulum membrane protein catalyzes the conversion of 7 α -hydroxy-4-cholesten-3-one into 7- α ,12- α -dihydroxy-4-cholesten-3-one. The balance between these two steroids determines the relative amounts of cholic acid and chenodeoxycholic acid both of which are secreted in the bile and affect the solubility of cholesterol. This gene is unique among the cytochrome P450 genes in that it is intronless.

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DBI: diazepam binding inhibitor (GABA receptor modulator, acyl-Coenzyme A binding protein)

5 Diazepam binding inhibitor (acyl-CoA-binding protein); binds and induces medium-chain acyl-CoA ester synthesis.

DEFA6: defensin, alpha 6, Paneth cell-specific

10 Defensins are a family of microbicidal and cytotoxic peptides thought to be involved in host defense. They are abundant in the granules of neutrophils and also found in the epithelia of mucosal surfaces such as those of the intestine, respiratory tract, urinary tract, and vagina. Members of the defensin family are highly similar in protein sequence and distinguished by a conserved cysteine motif. Several alpha defensin genes appear to be clustered on chromosome 8. The protein encoded by this
15 gene, defensin, alpha 6, is highly expressed in the secretory granules of Paneth cells of the small intestine, and likely plays a role in host defense of human bowel.

DEK: DEK oncogene (DNA binding)

20 Site-specific DNA binding protein; involved in transcriptional regulation and signal transduction.

DFNA5: deafness, autosomal dominant 5

25 Hearing impairment is a heterogeneous condition with over 40 loci described. The protein encoded by this gene is expressed in fetal cochlea, however, its function is not known. Nonsyndromic hearing impairment is associated with a mutation in this gene.

DGKD: diacylglycerol kinase, delta (130kD)

Diacylglycerol kinase delta; phosphorylates the arachidonoyl type of diacylglycerol; contains a pleckstrin homology domain and an EPH domain.

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DOCK1: dedicator of cyto-kinesis 1

Dedicator of cyto-kinesis 1 binds to the SH3 domain of CRK protein. It may regulate cell surface extension and may have a role in the cell surface extension of an engulfing cell around a dying cell during apoptosis.

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ECE1: endothelin converting enzyme 1

Endothelin converting enzyme; metalloprotease that regulates a peptide involved in vasoconstriction.

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E-Selectin (CD62E)

The endothelial leukocyte adhesion molecule-1 is expressed by cytokine-stimulated endothelial cells. It is thought to be responsible for the accumulation of blood leukocytes at sites of inflammation by mediating the adhesion of cells to the vascular lining. It exhibits structural features such as the presence of lectin- and EGF-like domains followed by short consensus repeat (SCR) domains that contain 6 conserved cysteine residues. These proteins are part of the selectin family of cell adhesion molecules. This gene is present in single copy in the human genome and contains 14 exons spanning about 13 kb of DNA. Adhesion molecules participate in the interaction between leukocytes and the endothelium and appear to be involved in the pathogenesis of atherosclerosis.

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ESR1: estrogen receptor 1

Estrogen receptor; nuclear receptor transcription factor activated by ligand-binding, involved in hormone-mediated inhibition of gene expression.

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ESR2: estrogen receptor 2 (ER beta)

Estrogen receptor beta 2; transcriptional activator involved in regulation of reproduction; exists in five isoforms.

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F2: coagulation factor II (thrombin)

Coagulation factor II is proteolytically cleaved to form thrombin in the first step of the coagulation cascade which ultimately results in the stemming of blood loss. F2 also plays a role in maintaining vascular integrity during development and postnatal life. Mutations in F2 leads to various forms of thrombosis and dysprothrombinemia.

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F3: coagulation factor III (thromboplastin, tissue factor)

This gene encodes coagulation factor III which is a cell surface glycoprotein. This factor enables cells to initiate the blood coagulation cascades, and it functions as the high-affinity receptor for the coagulation factor VII. The resulting complex provides a catalytic event that is responsible for initiation of the coagulation protease cascades by specific limited proteolysis. Unlike the other cofactors of these protease cascades, which circulate as nonfunctional precursors, this factor is a potent initiator that is fully functional when expressed on cell surfaces. There are 3 distinct domains of this factor: extracellular, transmembrane, and cytoplasmic. This protein is the only one in the coagulation pathway for which a congenital deficiency has not been described.

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F5: coagulation factor V (proaccelerin, labile factor)

This gene encodes coagulation factor V which is an essential factor of the blood coagulation cascade. This factor circulates in plasma, and is converted to the active form by the release of the activation peptide by thrombin during coagulation. This generates a heavy chain and a light chain which are held together by calcium ions. The active factor V is a cofactor that participates with activated coagulation factor X to activate prothrombin to thrombin. Defects in this gene result in either an autosomal recessive hemorrhagic diathesis or an autosomal dominant form of thrombophilia, which is known as activated protein C resistance.

F7: coagulation factor VII (serum prothrombin conversion accelerator)

This gene encodes coagulation factor VII which is a vitamin K-dependent factor essential for hemostasis. This factor circulates in the blood in a zymogen form, and is converted to an active form by either factor IXa, factor Xa, factor XIIa, or thrombin by minor proteolysis. Upon activation of the factor VII, a heavy chain containing a catalytic domain and a light chain containing 2 EGF-like domains are generated, and two chains are held together by a disulfide bond. In the presence of factor III and calcium ions, the activated factor then further activates the coagulation cascade by converting factor IX to factor IXa and/or factor X to factor Xa. Alternative splicing of this gene results in 2 transcripts. Defects in this gene can cause coagulopathy.

F9: coagulation factor IX (plasma thromboplastic component, Christmas disease, hemophilia B)

This gene encodes vitamin K-dependent coagulation factor IX that circulates in the blood as an inactive zymogen. This factor is converted to an active form by factor XIa, which excises the activation peptide and thus generates a heavy chain and a light chain held together by one or more disulfide bonds. The role of this activated factor IX in the blood coagulation cascade is to activate factor X to its active form through

interactions with Ca^{+2} ions, membrane phospholipids, and factor VIII. Alterations of this gene, including point mutations, insertions and deletions, cause factor IX deficiency, which is a recessive X-linked disorder, also called hemophilia B or Christmas disease.

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FABP3: fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)

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The intracellular fatty acid-binding proteins (FABPs) belongs to a multigene family. FABPs are divided into at least three distinct types, namely the hepatic-, intestinal- and cardiac-type. They form 14-15 kDa proteins and are thought to participate in the uptake, intracellular metabolism and/or transport of long-chain fatty acids. They may also be responsible in the modulation of cell growth and proliferation. Fatty acid-binding protein 3 gene contains four exons and its function is to arrest growth of mammary epithelial cells. This gene is a candidate tumor suppressor gene for human breast cancer.

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FACL3: fatty-acid-Coenzyme A ligase, long-chain 3

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The protein encoded by this gene is an isozyme of the long-chain fatty-acid-coenzyme A ligase family. Although differing in substrate specificity, subcellular localization, and tissue distribution, all isozymes of this family convert free long-chain fatty acids into fatty acyl-CoA esters, and thereby play a key role in lipid biosynthesis and fatty acid degradation. This isozyme is highly expressed in brain, and preferentially utilizes myristate, arachidonate, and eicosapentaenoate as substrates. The amino acid sequence of this isozyme is 92% identical to that of rat homolog.

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FACL4: fatty-acid-Coenzyme A ligase, long-chain 4

The protein encoded by this gene is an isozyme of the long-chain fatty-acid-coenzyme A ligase family. Although differing in substrate specificity, subcellular localization, and tissue distribution, all isozymes of this family convert free long-chain fatty acids into fatty acyl-CoA esters, and thereby play a key role in lipid biosynthesis and fatty acid degradation. This isozyme preferentially utilizes arachidonate as substrate. The absence of this enzyme may contribute to the mental retardation or Alport syndrome. Alternative splicing of this gene generates 2 transcript variants.

FMO1: flavin containing monooxygenase 1

Metabolic N-oxidation of the diet-derived amino-trimethylamine (TMA) is mediated by flavin-containing monooxygenase and is subject to an inherited FMO3 polymorphism in man resulting in a small subpopulation with reduced TMA N-oxidation capacity resulting in fish odor syndrome Trimethylaminuria. Three forms of the enzyme, FMO1 found in fetal liver, FMO2 found in adult liver, and FMO3 are encoded by genes clustered in the 1q23-q25 region. Flavin-containing monooxygenases are NADPH-dependent flavoenzymes that catalyzes the oxidation of soft nucleophilic heteroatom centers in drugs, pesticides, and xenobiotics.

GAA: glucosidase, alpha; acid (Pompe disease, glycogen storage disease type II)

This gene encodes acid alpha-glucosidase, which is essential for the degradation of glycogen to glucose in lysosomes. Different forms of acid alpha-glucosidase are obtained by proteolytic processing. Defects in this gene are the cause of glycogen storage disease II, also known as Pompe's disease, which is an autosomal recessive disorder with a broad clinical spectrum.

GAPD: glyceraldehyde-3-phosphate dehydrogenase

Glyceraldehyde-3-phosphate dehydrogenase catalyzes an important energy-yielding step in carbohydrate metabolism, the reversible oxidative phosphorylation of glyceraldehyde-3-phosphate in the presence of inorganic phosphate and nicotinamide adenine dinucleotide (NAD). The enzyme exists as a tetramer of identical chains. A GAPD pseudogene has been mapped to Xp21-p11 and 15 GAPD-like loci have been identified.

GARS: glycyl-tRNA synthetase

Aminoacyl-tRNA synthetases are a class of enzymes that charge tRNAs with their cognate amino acids. Glycyl-tRNA synthetase is an (α)₂ dimer which belongs to the class II family of tRNA synthetases. It has been shown to be a target of autoantibodies in the human autoimmune diseases, polymyositis or dermatomyositis.

GBE1: glucan (1,4- α -), branching enzyme 1 (glycogen branching enzyme, Andersen disease, glycogen storage disease type IV)

This monomeric enzyme functions in glycogen synthesis by catalyzing the formation of α 1,6- glucosidic linkages. It is most highly expressed in liver and muscle. Deficiency can result in glycogen storage disease IV (Andersen's disease).

GP6: glycoprotein VI (platelet)

Platelet glycoprotein VI; member of the paired Ig-like receptor family.

GPR-55

Member of the G protein-coupled receptor family.

GPRC5C: G protein-coupled receptor, family C, group 5, member C

The protein encoded by this gene is a member of the type 3 G protein-coupled receptor family. Members of this superfamily are characterized by a signature 7-transmembrane domain motif. The specific function of this protein is unknown; however, this protein may mediate the cellular effects of retinoic acid on the G protein signal transduction cascade. Alternative splicing in the 5' UTR of this gene results in two transcript variants.

3-hydroxy-3-methylglutaryl coenzyme A synthase

3-hydroxy-3-methylglutaryl-Coenzyme A synthase; functions in the first step in ketogenesis.

HK1: hexokinase 1

Hexokinases phosphorylate glucose to produce glucose-6-phosphate, thus committing glucose to the glycolytic pathway. This gene encodes a ubiquitous form of hexokinase which localizes to the outer membrane of mitochondria. Mutations in this gene have been associated with hemolytic anemia due to hexokinase deficiency. Alternative splicing of this gene results in five transcript variants which encode different isoforms, some of which are tissue-specific. Each isoform has a distinct N-terminus; the remainder of the protein is identical among all the isoforms. A sixth transcript variant has been described, but due to the presence of several stop codons, it is not thought to encode a protein.

HLA-B associated transcript 3 (BAT3)

A cluster of genes, BAT1-BAT5, has been localized in the vicinity of the genes for TNF alpha and TNF beta. These genes are all within the human major histocompatibility complex class III region. The protein encoded by this gene is a nuclear

protein. It has been implicated in the control of apoptosis and regulating heat shock protein. There are three alternatively spliced transcript variants described for this gene.

5 **HMGCL: 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase (hydroxymethylglutaricaciduria)**

3-Hydroxy-3-methylglutaryl coenzyme A lyase; cleaves 3-OH-3-methylglutaryl CoA to acetoacetic acid and acetyl CoA.

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HNF4A: hepatocyte nuclear factor 4, alpha

Nuclear hormone receptor transcription factor; regulates liver specific gene expression.

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Chromosome 12 BAC RP11-13J12

Cathepsin B

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Cathepsin B; lysosomal cysteine (thiol) protease that cleaves APP.

Chromosome 5 clone CTD-2235C13

Chromosome 7 clone RP11-351B12

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Cytochrome P450 3A locus

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The CYP3A locus includes all the known members of the 3A subfamily of the cytochrome P450 superfamily of genes. These genes encode monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. The CYP3A cluster consists of four genes, CYP3A43,

CYP3A4, CYP3A7 and CYP3A5. The region also contains two pseudogenes, CYP3A5P1 and CYP3A5P2, as well as several extra exons which may or may not be included in transcripts produced from this region. Previously another CYP3A member, CYP3A3, was thought to exist; however, it is now thought that this sequence represents a transcript variant of CYP3A4.

ITGB3

The ITGB3 protein product is the integrin beta chain beta 3. Integrins are integral cell-surface proteins composed of an alpha chain and a beta chain. A given chain may combine with multiple partners resulting in different integrins. Integrin beta 3 is found along with the alpha IIb chain in platelets. Integrins are known to participate in cell adhesion as well as cell-surface mediated signalling.

Methionine adenosyltransferase alpha subunit gene fragment.

MAT1A encodes methionine adenosyltransferase I (alpha isoform). MAT1A catalyzes the formation of S-adenosylmethionine from methionine and ATP. Both the beta and alpha isoforms may be encoded by MAT1A. Methionine adenosyltransferase deficiency is known to be caused by recessive as well as dominant mutations, the latter identified in autosomal dominant persistent hypermethioninemia.

Homo sapiens PAC clone RP1-102K2 from 22q12.1-qter

Homo sapiens partial ZNF202 gene for zinc finger protein homolog, exon 4

Zinc-finger protein 202 may repress genes involved in lipid metabolism; contains zinc fingers.

Homo sapiens vHNF1-C mRNA

Hepatocyte Nuclear Factor 1.

5 Human 2.5 kb mRNA for cytoskeletal tropomyosin TM30(nm)**Human c-kit gene**

10 KIT encodes the human homolog of the proto-oncogene c-kit. C-kit was first identified as the cellular homolog of the feline sarcoma viral oncogene v-kit. KIT is a type 3 transmembrane receptor for MGF (mast cell growth factor, also known as stem cell factor). Mutations in KIT are associated with gastrointestinal stromal tumors, mast cell disease, acute myelogenous leukemia, and piebaldism.

15 Human coagulation factor VII (F7) gene exon 1 and factor X (F10) gene, exon 1

This gene encodes coagulation factor VII which is a vitamin K-dependent factor essential for hemostasis. This factor circulates in the blood in a zymogen form, and is converted to an active form by either factor IXa, factor Xa, factor XIIa, or thrombin by minor proteolysis. Upon activation of the factor VII, a heavy chain containing a catalytic domain and a light chain containing 2 EGF-like domains are generated, and two chains are held together by a disulfide bond. In the presence of factor III and calcium ions, the activated factor then further activates the coagulation cascade by converting factor IX to factor IXa and/or factor X to factor Xa. Alternative splicing of this gene results in 2 transcripts. Defects in this gene can cause coagulopathy.

20
25

Human cytochrome P450 (CYP1A2) gene, exons 1 and 2

30 This gene, CYP1A2, encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and

other lipids. The protein encoded by this gene localizes to the endoplasmic reticulum and its expression is induced by some polycyclic aromatic hydrocarbons (PAHs), some of which are found in cigarette smoke. The enzyme's endogenous substrate is unknown; however, it is able to metabolize some PAHs to carcinogenic intermediates. Other xenobiotic substrates for this enzyme include caffeine, aflatoxin B1, and acetaminophen. The transcript from this gene contains four Alu sequences flanked by direct repeats in the 3' untranslated region. A related family member, CYP1A1, is located approximately 25 kb away from CYP1A2 on chromosome .

Human multidrug resistance-associated protein mRNA

See ABCC1.

Human succinyl CoA:3-oxoacid CoA transferase precursor (OXCT) mRNA

The mitochondrial matrix enzyme 3-oxoacid CoA transferase is homodimeric. It is a key enzyme in the extrahepatic utilization of ketone bodies, catalyzing the reversible transfer of coenzyme A from succinyl-CoA to acetoacetate, a necessary step in ketolytic energy production. Deficiencies can result in intermittent ketoacidosis.

Human T-lymphoma invasion and metastasis inducing TIAM1 protein (TIAM1) mRNA

Member of the GDP-GTP exchange factor family of proteins; modulates the activity of Rho-like proteins; has a Dbl homology and pleckstrin homology domains.

IL10: interleukin 10

Interleukin 10 (cytokine synthesis inhibitory factor); functions as a specific chemotactic factor for CD8+T cells.

IL17R: interleukin 17 receptor

Highly similar to murine Il17r; may play a role in T cell activation and induction of IL-2 (Il2).

5

IL3: interleukin 3 (colony-stimulating factor, multiple)

Interleukin-3 (colony-stimulating factor); plays a role in hematopoiesis; member of a family of growth factors.

10

IL6: interleukin 6 (interferon, beta 2)

Interleukin 6 (interferon-beta 2); induces the maturation of B cells into immunoglobulin-secreting cells.

15

IL8RA: interleukin 8 receptor, alpha

Interleukin 8 receptor alpha; G protein-coupled receptor that mediates neutrophil chemotaxis and binds interleukin 8 (IL8).

20

INHBC: inhibin, beta C

This gene encodes the beta C chain of inhibin, a member of the TGF-beta superfamily. This subunit forms heterodimers with beta A and beta B subunits. Inhibins and activins, also members of the TGF-beta superfamily, are hormones with opposing actions and are involved in hypothalamic, pituitary, and gonadal hormone secretion, as well as growth and differentiation of various cell types.

25

ITGAL: integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide)

5 ITGAL encodes the integrin alpha L chain. Integrins are heterodimeric integral membrane proteins composed of an alpha chain and a beta chain. This I-domain containing alpha integrin combines with the beta 2 chain (ITGB2) to form the integrin lymphocyte function-associated antigen-1 (LFA-1), which is expressed on all leukocytes. LFA-1 plays a central role in leukocyte intercellular adhesion through interactions with its ligands, ICAMs 1-3 (intercellular adhesion molecules 1 through
10 3), and also functions in lymphocyte costimulatory signaling.

ITGB2: integrin, beta 2 (antigen CD18 (p95), lymphocyte function-associated antigen 1; macrophage antigen 1 (mac-1) beta subunit)

15 The ITGB2 protein product is the integrin beta chain beta 2. Integrins are integral cell-surface proteins composed of an alpha chain and a beta chain. A given chain may combine with multiple partners resulting in different integrins. For example, beta 2 combines with the alpha L chain to form the integrin LFA-1, and combines with the alpha M chain to form the integrin Mac-1. Integrins are known to participate
20 in cell adhesion as well as cell-surface mediated signalling.

KCNQ1: potassium voltage-gated channel, KQT-like subfamily, member 1

25 KCNQ1 encodes the K⁺ channel subunit responsible for the delayed-rectifier K⁺ current in cardiac myocytes. The delayed-rectifier channel is completed by the protein encoded by KCNE1. Mutations in KCNQ1 cause inherited long-QT syndrome.

LAMA3: laminin, alpha 3 (nicein (150kD), kalinin (165kD), BM600 (150kD), epilegrin)

5 Laminins are basement membrane components thought to mediate the attachment, migration and organization of cells into tissues during embryonic development by interacting with other extracellular matrix components. The protein encoded by this gene is the alpha-3 chain of laminin 5, which is a complex glycoprotein composed of three subunits (alpha, beta, and gamma). Laminin 5 is thought to be involved in cell adhesion, signal transduction and differentiation of keratinocytes. Mutations in this
10 gene have been identified as the cause of Herlitz type junctional epidermolysis bullosa. Alternative splicing has been observed at this locus but the full-length nature of these variants has not been determined.

LAMR1: laminin receptor 1 (67kD, ribosomal protein SA)

15 Laminins, a family of extracellular matrix glycoproteins, are the major non-collagenous constituent of basement membranes. They have been implicated in a wide variety of biological processes including cell adhesion, differentiation, migration, signaling, neurite outgrowth and metastasis. Many of the effects of
20 laminin are mediated through interactions with cell surface receptors. These receptors include members of the integrin family, as well as non-integrin laminin-binding proteins. This gene encodes a high-affinity, non-integrin family, laminin receptor 1. This receptor has been variously called 67 kD laminin receptor, 37 kD laminin receptor precursor (37LRP) and p40 ribosome-associated protein. The amino acid
25 sequence of laminin receptor 1 is highly conserved through evolution, suggesting a key biological function. It has been observed that the level of the laminin receptor transcript is higher in colon carcinoma tissue and lung cancer cell line than their normal counterparts. Also, there is a correlation between the upregulation of this polypeptide in cancer cells and their invasive and metastatic phenotype. Multiple
30 copies of this gene exist, however, most of them are pseudogenes thought to have arisen from retropositional events..

LDLR: low density lipoprotein receptor (familial hypercholesterolemia)

5 The low density lipoprotein receptor (LDLR) gene family consists of cell surface proteins involved in receptor-mediated endocytosis of specific ligands. Low density lipoprotein (LDL) is normally bound at the cell membrane and taken into the cell ending up in lysosomes where the protein is degraded and the cholesterol is made available for repression of microsomal enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol synthesis. 10 At the same time, a reciprocal stimulation of cholesterol ester synthesis takes place. Mutations in the LDL receptor (LDLR) gene cause the autosomal dominant disorder, familial hypercholesterolemia.

LGALS7: lectin, galactoside-binding, soluble, 7 (galectin 7)

15 The galectins are a family of beta-galactoside-binding proteins implicated in modulating cell-cell and cell-matrix interactions. Differential and in situ hybridizations indicate that this lectin is specifically expressed in keratinocytes. It is expressed at all stages of epidermal differentiation (i.e., in basal and suprabasal layers). It is moderately repressed by retinoic acid. The protein was found mainly in stratified squamous epithelium. The antigen localized to basal keratinocytes, although it was also found, albeit at lower levels, in the suprabasal layers where it concentrated to areas of cell-to-cell contact. The cellular localization and its striking down-regulation in cultured keratinocytes imply a role in cell-cell and/or cell-matrix 25 interactions necessary for normal growth control.

LIMK1: LIM domain kinase 1

30 There are approximately 40 known eukaryotic LIM proteins, so named for the LIM domains they contain. LIM domains are highly conserved cysteine-rich structures containing 2 zinc fingers. Although zinc fingers usually function by binding to DNA

or RNA, the LIM motif probably mediates protein-protein interactions. LIM kinase-1 and LIM kinase-2 belong to a small subfamily with a unique combination of 2 N-terminal LIM motifs and a C-terminal protein kinase domain. LIMK1 is likely to be a component of an intracellular signaling pathway and may be involved in brain development. LIMK1 hemizyosity is implicated in the impaired visuospatial constructive cognition of Williams syndrome. Two splice variant have been identified.

LMNB2: lamin B2

Lamin B2; member of a family of structural nuclear envelope proteins.

LPL: lipoprotein lipase

LPL encodes lipoprotein lipase, which is expressed in heart, muscle, and adipose tissue. LPL functions as a homodimer, and has the dual functions of triglyceride hydrolase and ligand/bridging factor for receptor-mediated lipoprotein uptake. Severe mutations that cause LPL deficiency result in type I hyperlipoproteinemia, while less extreme mutations in LPL are linked to many disorders of lipoprotein metabolism.

LRP8: low density lipoprotein receptor-related protein 8, apolipoprotein E receptor

This gene encodes an apolipoprotein E receptor, a member of the low density lipoprotein receptor (LDLR) family. Apolipoprotein E is a small lipophilic plasma protein and a component of lipoproteins such as chylomicron remnants, very low density lipoprotein (VLDL), and high density lipoprotein (HDL). The apolipoprotein E receptor is involved in cellular recognition and internalization of these lipoproteins. Alternative splicing generates three transcript variants for this gene; additional variants have been described, but their full length nature has not been determined.

- 50 -

LSS: lanosterol synthase (2,3-oxidosqualene-lanosterol cyclase)

Lanosterol synthase ((S)-2,3-epoxysqualene mutase); catalyzes the cyclization of (S)-2,3-oxidosqualene; forms lanosterol during sterol biosynthesis.

5

LTA: lymphotoxin alpha (TNF superfamily, member 1)

Lymphotoxin alpha, a member of the tumor necrosis factor family, is a cytokine produced by lymphocytes. LTA is highly inducible, secreted, and exists as homotrimeric molecule. LTA forms heterotrimers with lymphotoxin-beta which anchors lymphotoxin-alpha to the cell surface. LTA mediates a large variety of inflammatory, immunostimulatory, and antiviral responses. LTA is also involved in the formation of secondary lymphoid organs during development and plays a role in apoptosis.

10

15

MAOA: monoamine oxidase A

MAOA encodes monoamine oxidase A, an enzyme that degrades amine neurotransmitters, such as dopamine, norepinephrine, and serotonin. Deficiency of this enzyme results in Brunner syndrome.

20

MARCKS: myristoylated alanine-rich protein kinase C substrate

The protein encoded by this gene is a substrate for protein kinase C. It is localized to the plasma membrane and is an actin filament crosslinking protein. Phosphorylation by protein kinase C or binding to calcium-calmodulin inhibits its association with actin and with the plasma membrane, leading to its presence in the cytoplasm. The protein is thought to be involved in cell motility, phagocytosis, membrane trafficking and mitogenesis.

25

30

MCL1: myeloid cell leukemia sequence 1 (BCL2-related)

Similar to BCL2.

5 **MCP: membrane cofactor protein (CD46, trophoblast-lymphocyte cross-reactive antigen)**

Membrane cofactor protein; acts as the receptor for the measles virus, may be involved in the regulation of complement activation; contains SCRs.

10

METTL1: methyltransferase-like 1

15

This gene is an ortholog of the *S. cerevisiae* YDL201w gene, which is predicted to encode a methyltransferase. The gene product contains a conserved S-adenosyl-methionine-binding motif, which is typical of a methyltransferase. Alternative splice variants encoding different protein isoforms and transcript variants utilizing alternative polyA sites have been described in the literature.

20

MLLT3: myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, *Drosophila*);

Serine and proline rich protein, has a nuclear targeting sequence.

25

MTHFD1: methylenetetrahydrofolate dehydrogenase (NADP+ dependent), methenyltetrahydrofolate cyclohydrolase, formyltetrahydrofolate synthetase

30

This gene encodes a protein that possesses three distinct enzymatic activities, 5,10-methylenetetrahydrofolate dehydrogenase, 5,10-methenyltetrahydrofolate cyclohydrolase and 10-formyltetrahydrofolate synthetase. Each of these activities catalyzes one of three sequential reactions in the interconversion of 1-carbon derivatives of tetrahydrofolate, which are substrates for methionine, thymidylate, and

de novo purine syntheses. The trifunctional enzymatic activities are conferred by two major domains, an aminoterminal portion containing the dehydrogenase and cyclohydrolase activities and a larger synthetase domain.

5 **MTMR2 myotubularin related protein 2 (MTMR2)**

This gene is a member of the myotubularin family and encodes a putative tyrosine phosphatase. Mutations in this gene are a cause of Charcot-Marie-Tooth disease type 4B, an autosomal recessive demyelinating neuropathy. This gene utilizes multiple
10 polyA signals, only one of which has been determined.

Muscle specific serine kinase (MSSK1; serine/threonine kinase 23, STK23),

Highly similar to SRPK2; may be protein kinase for SR family of RNA splicing
15 factors; contains a kinase domain.

MVD: mevalonate (diphospho) decarboxylase

The enzyme mevalonate pyrophosphate decarboxylase catalyzes the conversion of
20 mevalonate pyrophosphate into isopentenyl pyrophosphate in one of the early steps in cholesterol biosynthesis. It decarboxylates and dehydrates its substrate while hydrolyzing ATP.

MYH11: myosin, heavy polypeptide 11, smooth muscle

25 The protein encoded by this gene is a smooth muscle myosin belonging to the myosin heavy chain family. The gene product is a subunit of a hexameric protein that consists of 2 heavy chain subunits and 2 pairs of non-identical light chain subunits. It functions as a major contractile protein, converting chemical energy into mechanical
30 energy through the hydrolysis of ATP. The gene encoding a human ortholog of rat NUDE1 is transcribed from the reverse strand of MYH11 gene, and its 3' end

overlaps with that of the latter. The pericentric inversion of chromosome 16 [inv(16)(p13q22)] produces a chimeric transcript consisting of the first 165 residues from the N terminus of core-binding factor beta in a fusion with the C-terminal portion of the smooth muscle myosin heavy chain. This chromosomal rearrangement is associated with acute myeloid leukemia of the M4Eo subtype. Alternative splicing generates isoforms that are differentially expressed, with ratios changing during muscle cell maturation. Additional splice variants have been described but their full-length nature has not been determined..

MYH7: myosin, heavy polypeptide 7, cardiac muscle, beta

MYH7 encodes the cardiac muscle beta (or slow) isoform of myosin. Changes in the relative abundance of MYH7 and MYH6 (the alpha, or fast, isoform of cardiac myosin heavy chain) correlate with the contractile velocity of cardiac muscle. Mutations in MYH7 are associated with familial hypertrophic cardiomyopathy.

**NADH dehydrogenase (ubiquinone) 1, alpha subcomplex, 4 (9kD, MLRQ),
NDUFA4**

Subunit of NADH-ubiquinone oxidoreductase (complex I); transports electrons from NADH to ubiquinone.

NADH-UBIQUINONE OXIDOREDUCTASE CHAIN 5 (EC 1.6.5.3).

Subunit of NADH-ubiquinone oxidoreductase (complex I); transports electrons from NADH to ubiquinone.

NDUFA9: NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9 (39kD)

NGFB: nerve growth factor, beta polypeptide

5 Nerve growth factor beta; has roles in neuronal differentiation and survival.

NGFR: nerve growth factor receptor (TNFR superfamily, member 16)

10 Nerve growth factor receptor contains an extracellular domain containing four 40-amino acid repeats with 6 cysteine residues at conserved positions followed by a serine/threonine-rich region, a single transmembrane domain, and a 155-amino acid cytoplasmic domain. The cysteine-rich region contains the nerve growth factor binding domain.

15 **NID2: nidogen 2**

Nidogen-2; basement membrane protein,.

HSU15552: acidic 82 kDa protein mRNA

20

Nonmuscle type myosin heavy chain 9 (MYH9)

25 Non-muscle myosin heavy chain 9; motor protein that provides force for muscle contraction, cytokinesis and phagocytosis; contains an ATPase head domain and a rod-like tail domain.

NPC1: Niemann-Pick disease, type C1

30 NPC1 was identified as the gene that when mutated, results in Niemann-Pick C disease. NPC1 encodes a putative integral membrane protein containing motifs

consistent with a role in intracellular transport of cholesterol to post-lysosomal destinations.

Nth endonuclease III-like 1 (NTHL1)

5

Endonuclease; excises damaged pyrimidines.

NUCB2: nucleobindin 2

10

Nucleobindin 2; may bind DNA and calcium; has DNA-binding and EF-hand domains, and a leucine-zipper.

nuclear receptor subfamily 1, group I, member 2 (NR1I2)

15

The gene product belongs to the nuclear receptor superfamily, members of which are transcription factors characterized by a ligand-binding domain and a DNA-binding domain. The encoded protein is a transcriptional regulator of the cytochrome P450 gene CYP3A4, binding to the response element of the CYP3A4 promoter as a heterodimer with the 9-cis retinoic acid receptor RXR. It is activated by a range of compounds that induce CYP3A4, including dexamethasone and rifampicin. The gene product contains a zinc finger domain. Three alternatively spliced transcripts that encode different isoforms have been described, one of which encodes two products through the use of alternative translation initiation codons. Additional transcript variants derived from alternative promoter usage, alternative splicing, and/or alternative polyadenylation exist, but they have not been fully described.

20

25

OGDH: oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide)

30

Alpha-ketoglutarate or 2-oxoglutarate dehydrogenase; helps convert a-ketoglutarate to succinyl coenzyme A in Krebs cycle.

OXCT: 3-oxoacid CoA transferase

The mitochondrial matrix enzyme 3-oxoacid CoA transferase is homodimeric. It is a key enzyme in the extrahepatic utilization of ketone bodies, catalyzing the reversible transfer of coenzyme A from succinyl-CoA to acetoacetate, a necessary step in ketolytic energy production. Deficiencies can result in intermittent ketoacidosis.

P2RY1: purinergic receptor P2Y, G-protein coupled, 1

Purinergic receptor P2Y1, a G protein-coupled receptor; mediates responses to ATP and increases inositol phosphate levels.

PCCA: propionyl Coenzyme A carboxylase, alpha polypeptide

PCCA encodes the alpha subunit of the heterodimeric mitochondrial enzyme Propionyl-CoA carboxylase. PCCA encodes the biotin-binding region of this enzyme. Mutations in either PCCA or PCCB (encoding the beta subunit) lead to an enzyme deficiency result in propionic acidemia.

PDGFB: platelet-derived growth factor beta polypeptide (simian sarcoma viral (v-sis) oncogene homolog)

The protein encoded by this gene is a member of the platelet-derived growth factor family. The four members of this family are mitogenic factors for cells of mesenchymal origin and are characterized by a motif of eight cysteines. This gene product can exist either as a homodimer or as a heterodimer with the platelet-derived growth factor alpha polypeptide, where the dimers are connected by disulfide bonds. Mutations in this gene are associated with meningioma. Reciprocal translocations between chromosomes 22 and 7, at sites where this gene and that for COL1A1 are located, are associated with a particular type of skin tumor called dermatofibro-

sarcoma protuberans resulting from unregulated expression of growth factor. Two splice variants have been identified for this gene.

PERIOD CIRCADIAN PROTEIN 2 (KIAA0347)

5

This gene is a member of the Period family of genes and is expressed in a circadian pattern in the suprachiasmatic nucleus, the primary circadian pacemaker in the mammalian brain. Genes in this family encode components of the circadian rhythms of locomotor activity, metabolism, and behavior. Circadian expression in the suprachiasmatic nucleus continues in constant darkness, and a shift in the light/dark cycle evokes a proportional shift of gene expression in the suprachiasmatic nucleus. The specific function of this gene is not yet known.

10

Peroxisome proliferative activated receptor, delta (PPARD)

15

Peroxisome proliferator-activated receptor delta is a member of the steroid hormone receptor superfamily.

PGM5: phosphoglucomutase 5

20

Phosphoglucomutase-related (aciculin) putative structural protein; interacts with the cytoskeletal proteins dystrophin and utrophin.

PLA2G3: phospholipase A2, group III

25

Group III secreted phospholipase A2; calcium-dependent, displays a preference for phosphatidylglycerol over phosphatidylcholine.

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PLA2G4C: phospholipase A2, group IVC (cytosolic, calcium-independent)

Group IVC calcium-independent phospholipase a2; hydrolyzes the phospholipid sn-2 ester bond; member of the phospholipase family.

5

PLA2G6: phospholipase A2, group VI (cytosolic, calcium-independent)

Cytosolic calcium-independent phospholipase_a2; hydrolyzes the phospholipid sn-2 ester bond; member of the phospholipase family.

10

PMVK: phosphomevalonate kinase

Phosphomevalonate kinase; converts mevalonate-5-phosphate to mevalonate-5-diphosphate.

15

PNMT: phenylethanolamine N-methyltransferase

Phenylethanolamine N-methyltransferase; converts norepinephrine to epinephrine.

20

PON1: paraoxonase 1**PON2: paraoxonase 2**

25

Paraoxonase/arylesterase 2; possibly functions in protecting low density lipoprotein against oxidative modification; member of a family that hydrolyzes toxic organophosphates.

PPARA: peroxisome proliferative activated receptor, alpha

30

Peroxisome proliferators are a diverse group of chemicals which include hypolipidemic drugs, herbicides, leukotriene antagonists, and plasticizers, and are so

called because they induce an increase in the size and number of peroxisomes. Peroxisomes are subcellular organelles found in plants and animals, and contain enzymes for respiration, cholesterol and lipid metabolism. Infact, the fibrate class of hypolipidemic drugs is used to reduce triglycerides and cholesterol in patients with hyperlipidemia, a major risk factor for coronary heart disease. The action of peroxisome proliferators is thought to be mediated via specific receptors belonging to the steroid hormone receptor superfamily, called PPARs. Thus far, four closely related subtypes, alpha, beta, gamma and delta, have been identified. The subtype PPAR-alpha, encoded by PPARG, is a nuclear transcription factor. Upon activation by peroxisome proliferators, it modulates the expression of target genes involved in lipid metabolism, suggesting a role for PPAR-alpha in lipid homeostasis..

PPARG: peroxisome proliferative activated receptor, gamma

The protein encoded by this gene is a member of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors. PPARs form heterodimers with retinoid X receptors (RXRs) and these heterodimers regulate transcription of various genes. Three subtypes of PPARs are known: PPAR-alpha, PPAR-delta, and PPAR-gamma. The protein encoded by this gene is PPAR-gamma and is a regulator of adipocyte differentiation. Additionally, PPAR-gamma has been implicated in the pathology of numerous diseases including obesity, diabetes, atherosclerosis and cancer. Multiple transcript variants that use alternate promoters and splicing have been identified for this gene. At least three of these variants encode the same isoform.

PPM1A: protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform

Magnesium- or manganese-dependent alpha protein phosphatase 1A; regulates cell stress responses.

PROBABLE G PROTEIN-COUPLED RECEPTOR APJ.**PTPRA: protein tyrosine phosphatase, receptor type, A**

5 The protein encoded by this gene is a member of the protein tyrosine phosphatase (PTP) family. PTPs are known to be signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. This PTP contains an extracellular domain, a single transmembrane segment and two tandem intracytoplasmic catalytic domains, and thus represents a
10 receptor-type PTP. This PTP has been shown to dephosphorylate and activate Src family tyrosine kinases, and is implicated in the regulation of integrin signaling, cell adhesion and proliferation. Three alternatively spliced variants of this gene, which encode two distinct isoforms, have been reported.

15 **PYGM: phosphorylase, glycogen; muscle (McArdle syndrome, glycogen storage disease type V)**

Muscle glycogen phosphorylase.

20 **RTN1: reticulon 1**

RXRA: retinoid X receptor, alpha

25 Retinoid X receptors (RXRs) and retinoic acid receptors (RARs), are nuclear receptors that mediate the biological effects of retinoids by their involvement in retinoic acid-mediated gene activation. These receptors exert their action by binding, as homodimers or heterodimers, to specific sequences in the promoters of target genes and regulating their transcription. The protein encoded by this gene is a
30 member of the steroid and thyroid hormone receptor superfamily of transcriptional regulators.

RXRB: retinoid X receptor, beta

Retinoid X receptor beta; binds to and serves as transcriptional coactivator for retinoic acid.

5

SCA1: spinocerebellar ataxia 1 (olivopontocerebellar ataxia 1, autosomal dominant, ataxin 1)

10 The autosomal dominant cerebellar ataxias (ADCA) are a heterogeneous group of neurodegenerative disorders characterized by progressive degeneration of the cerebellum, brain stem and spinal cord. Clinically, ADCA has been divided into three groups: ADCA types I-III. ADCAI is genetically heterogeneous, with five genetic loci, designated spinocerebellar ataxia (SCA) 1, 2, 3, 4 and 6, being assigned to five different chromosomes. ADCAII, which always presents with retinal
15 degeneration (SCA7), and ADCAIII often referred to as the 'pure' cerebellar syndrome (SCA5), are most likely homogeneous disorders. Several SCA genes have been cloned and shown to contain CAG repeats in their coding regions. ADCA is caused by the expansion of the CAG repeats, producing an elongated polyglutamine tract in the corresponding protein. The expanded repeats are variable in size and
20 unstable, usually increasing in size when transmitted to successive generations. The function of the ataxins is not known. The SCA1 locus has been mapped to chromosome 6, and it has been determined that the diseased allele contains 41-81 CAG repeats, compared to 6-39 in the normal allele. Several transcript variants of SCA1 in the 5' UTR have been described; however, their full-length nature is not
25 known..

SDF1: stromal cell-derived factor 1

30 Stromal cell-derived factor 1; lymphocyte chemoattractant that signals through the receptor CXCR4.

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SERPINA5: serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 5

5 Protein C inhibitor (plasminogen activator inhibitor III); may be a serine protease inhibitor; member of the serpin family of serine protease inhibitors.

SERPINH1: serine (or cysteine) proteinase inhibitor, clade H (heat shock protein 47), member 1, (collagen binding protein 1)

10 Colligin; collagen-binding protein; Similar to HSPs and to serpin family serine protease inhibitors.

SLC21A6: solute carrier family 21 (organic anion transporter), member 6

15 Organic anion transporter.

SLC27A1: solute carrier family 27 (fatty acid transporter), member 1

SULT1A2: sulfotransferase family, cytosolic, 1A, phenol-preferring, member 2

20 Phenol-metabolizing sulfotransferase 2; sulfonates simple planar phenols.

THBS3: Thrombospondin 3

25 Thrombospondin 3 binds heparin and calcium; similar to murine Thbs3

TBP: TATA box binding protein

30 TATA box binding protein, component of the TFIID complex; functions in the initiation of mRNA synthesis and basal transcription.

TBXA2R: thromboxane A2 receptor

Thromboxane A2 receptor (prostaglandin H2 receptor); G protein-coupled receptor, activates Ca²⁺-activated chloride channels; stimulates platelet aggregation and smooth muscle constriction.

TCF2: transcription factor 2, hepatic; LF-B3; variant hepatic nuclear factor

TCF2 encodes transcription factor 2, a liver-specific factor of the homeobox-containing basic helix-turn-helix family. The TCF2 protein is believed to form heterodimers with another liver-specific member of this transcription factor family, TCF1; depending on the TCF2 isoform, the result may be to activate or inhibit transcription of target genes. Mutation of TCF2 that disrupts normal function has been identified as the cause of MODY5 (Maturity-Onset of Diabetes, Type 5). A third human transcript variant is believed to exist based on such a variant in the rat; however, to date such an mRNA species has not been isolated.

TETTRAN: tetracycline transporter-like protein

Similar to E. coli tetracycline resistance efflux protein.

TGFB1: transforming growth factor, beta 1 (Camurati-Engelmann disease)

Transforming growth factor-beta 1; regulates cell proliferation, differentiation, and apoptosis.

TGFB2: transforming growth factor, beta 2

Transforming growth factor-beta 2 (glioblastoma-derived T cell suppressor factor); suppresses IL2 - dependent growth of T cells; member of a family of cytokines that transmits signals through transmembrane serine/threonine kinases.

TGFB3: transforming growth factor, beta 3

5 Transforming growth factor-beta 3; transmits signals through transmembrane serine/threonine kinases, may be required for normal development of the lung and palate; member of family of cytokines, very strongly similar to murine Tgfb3.

THPO: thrombopoietin (myeloproliferative leukemia virus oncogene ligand, megakaryocyte growth and development factor)

10

Thrombopoietin; binds to c-Mpl receptor and regulates megakaryocyte development.

TNFAIP2: tumor necrosis factor, alpha-induced protein 2

15 Secreted by vascular endothelium, expression is induced by tumor necrosis factor alpha, interleukin-1 beta, and lipopolysaccharide.

TRAP1: heat shock protein 75

20 Heat shock protein 75; binds and refolds denatured RB1 during M phase and after heat shock; member of the HSP90 family of molecular chaperones.

TRIP10: thyroid hormone receptor interactor 10

25 Similar to the non-kinase domains of FER and Fes/Fps tyrosine kinases; binds to activated Cdc42 and may regulate actin cytoskeleton; contains an SH3 domain.

TXN: thioredoxin

30 Thioredoxin; has dithiol-disulfide oxidoreductase activity.

USP6: ubiquitin specific protease 6 (Tre-2 oncogene)

Ubiquitin specific protease 6 (Tre-2 oncogene); cleaves ubiquitin from proteins, has predicted nucleic acid-binding properties.

5

UTRN: utrophin (homologous to dystrophin)

This gene shares both structural and functional similarities with the dystrophin gene. It contains an actin-binding N-terminus, a triple coiled-coil repeat central region, and a C-terminus that consists of protein-protein interaction motifs which interact with dystroglycan protein components. The protein encoded by this gene is located at the neuromuscular synapse and myotendinous junctions, where it participates in post-synaptic membrane maintenance and acetylcholine receptor clustering. Mouse studies suggest that this gene may serve as a functional substitute for the dystrophin gene and therefore, may serve as a potential therapeutic alternative to muscular dystrophy which caused by mutations in the dystrophin gene. Alternative splicing of the utrophin gene has been described; however, the full-length nature of these variants has not yet been determined.

10

15

20 VEGF: vascular endothelial growth factor

Vascular endothelial growth factor; induces endothelial cell proliferation and vascular permeability.

25 VEGFB: vascular endothelial growth factor B

Vascular endothelial growth factor B; involved in angiogenesis and endothelial cell growth.

WISP1: WNT1 inducible signaling pathway protein 1

This gene encodes a member of the WNT1 inducible signaling pathway (WISP) protein subfamily, which belongs to the connective tissue growth factor (CTGF) family. WNT1 is a member of a family of cysteine-rich, glycosylated signaling proteins that mediate diverse developmental processes. The CTGF family members are characterized by four conserved cysteine-rich domains: insulin-like growth factor-binding domain, von Willebrand factor type C module, thrombospondin domain and C-terminal cystine knot-like domain. This gene may be downstream in the WNT1 signaling pathway that is relevant to malignant transformation. It is expressed at a high level in fibroblast cells, and overexpressed in colon tumors. The encoded protein binds to decorin and biglycan, two members of a family of small leucine-rich proteoglycans present in the extracellular matrix of connective tissue, and possibly prevents the inhibitory activity of decorin and biglycan in tumor cell proliferation. It also attenuates p53-mediated apoptosis in response to DNA damage through activation of the Akt kinase. It is 83% identical to the mouse protein at the amino acid level. Alternative splicing of this gene generates 2 transcript variants..

XDH: xanthine dehydrogenase

Xanthine dehydrogenase belongs to the group of molybdenum-containing hydroxylases involved in the oxidative metabolism of purines. The enzyme is a homodimer. Xanthine dehydrogenase can be converted to xanthine oxidase by reversible sulfhydryl oxidation or by irreversible proteolytic modification. Defects in xanthine dehydrogenase cause xanthinuria, may contribute to adult respiratory stress syndrome, and may potentiate influenza infection through an oxygen metabolite-dependent mechanism. .

YAP1: Yes-associated protein 1, 65 kD

Yes-associated protein; binds to the proto-oncoprotein Yes; has a WW domain.

5 PROCR: protein C receptor, endothelial (EPCR)

Endothelial Protein C receptor; binds protein C in a calcium-dependent manner; member of the CD1/major histocompatibility complex superfamily.

10 STX1A: syntaxin 1A (brain)

Syntaxin 1A (brain); involved in intracellular transport and neurotransmitter release.

As SNPs are linked to other SNPs in neighboring genes on a chromosome (Linkage
15 Disequilibrium) those SNPs could also be used as marker SNPs. In a recent
publication it was shown that SNPs are linked over 100 kb in some cases more than
150 kb (Reich D.E. et al. Nature 411, 199-204, 2001). Hence SNPs lying in regions
neighbouring PA SNPs could be linked to the latter and by this being a diagnostic
marker. These associations could be performed as described for the gene
20 polymorphism in methods.

Definitions

For convenience, the meaning of certain terms and phrases employed in the
25 specification, examples, and appended claims are provided below. Moreover, the
definitions by itself are intended to explain a further background of the invention.

The term "allele", which is used interchangeably herein with "allelic variant" refers
to alternative forms of a gene or portions thereof. Alleles occupy the same locus or
30 position on homologous chromosomes. When a subject has two identical alleles of a
gene, the subject is said to be homozygous for the gene or allele. When a subject has

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two different alleles of a gene, the subject is said to be heterozygous for the gene. Alleles of a specific gene can differ from each other in a single nucleotide, or several nucleotides, and can include substitutions, deletions, and insertions of nucleotides. An allele of a gene can also be a form of a gene containing a mutation.

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The term "allelic variant of a polymorphic region of a gene" refers to a region of a gene having one of several nucleotide sequences found in that region of the gene in other individuals.

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"Homology" or "identity" or "similarity" refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. An "unrelated" or "non-homologous" sequence shares less than 40% identity, though preferably less than 25% identity, with one of the sequences of the present invention.

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The term "a homologue of a nucleic acid" refers to a nucleic acid having a nucleotide sequence having a certain degree of homology with the nucleotide sequence of the nucleic acid or complement thereof. A homologue of a double stranded nucleic acid having SEQ ID NO. X is intended to include nucleic acids having a nucleotide sequence which has a certain degree of homology with SEQ ID NO. X or with the complement thereof. Preferred homologous of nucleic acids are capable of hybridizing to the nucleic acid or complement thereof.

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The term "interact" as used herein is meant to include detectable interactions between molecules, such as can be detected using, for example, a hybridization assay.

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The term interact is also meant to include "binding" interactions between molecules. Interactions may be, for example, protein-protein, protein-nucleic acid, protein-small molecule or small molecule-nucleic acid in nature.

5 The term "intronic sequence" or "intronic nucleotide sequence" refers to the nucleotide sequence of an intron or portion thereof.

10 The term "isolated" as used herein with respect to nucleic acids, such as DNA or RNA, refers to molecules separated from other DNAs or RNAs, respectively, that are present in the natural source of the macromolecule. The term isolated as used herein also refers to a nucleic acid or peptide that is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized.

15 Moreover, an "isolated nucleic acid" is meant to include nucleic acid fragments which are not naturally occurring as fragments and would not be found in the natural state. The term "isolated" is also used herein to refer to polypeptides which are isolated from other cellular proteins and is meant to encompass both purified and recombinant polypeptides.

20 The term "lipid" shall refer to a fat or fat-like substance that is insoluble in polar solvents such as water. The term "lipid" is intended to include true fats (e.g. esters of fatty acids and glycerol); lipids (phospholipids, cerebroside, waxes); sterols (cholesterol, ergosterol) and lipoproteins (e.g. HDL, LDL and VLDL).

25 The term "locus" refers to a specific position in a chromosome. For example, a locus of a gene refers to the chromosomal position of the gene.

30 The term "modulation" as used herein refers to both up-regulation, (i.e., activation or stimulation), for example by agonizing, and down-regulation (i.e. inhibition or

suppression), for example by antagonizing of a bioactivity (e.g. expression of a gene).

5 The term "molecular structure" of a gene or a portion thereof refers to the structure as defined by the nucleotide content (including deletions, substitutions, additions of one or more nucleotides), the nucleotide sequence, the state of methylation, and/or any other modification of the gene or portion thereof.

10 The term "mutated gene" refers to an allelic form of a gene, which is capable of altering the phenotype of a subject having the mutated gene relative to a subject which does not have the mutated gene. If a subject must be homozygous for this mutation to have an altered phenotype, the mutation is said to be recessive. If one copy of the mutated gene is sufficient to alter the genotype of the subject, the mutation is said to be dominant. If a subject has one copy of the mutated gene and
15 has a phenotype that is intermediate between that of a homozygous and that of a heterozygous (for that gene) subject, the mutation is said to be co-dominant.

As used herein, the term "nucleic acid" refers to polynucleotides such as deoxy-
ribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). The term
20 should also be understood to include, as equivalents, derivatives, variants and analogs of either RNA or DNA made from nucleotide analogs, including peptide nucleic acids (PNA), morpholino oligonucleotides (J. Summerton and D. Weller, Antisense and Nucleic Acid Drug Development 7:187 (1997)) and, as applicable to the embodiment being described, single (sense or antisense) and double-stranded
25 polynucleotides. Deoxyribonucleotides include deoxyadenosine, deoxycytidine, deoxyguanosine, and deoxythymidine. For purposes of clarity, when referring herein to a nucleotide of a nucleic acid, which can be DNA or an RNA, the term "adenosine", "cytidine", "guanosine", and "thymidine" are used. It is understood that if the nucleic acid is RNA, a nucleotide having a uracil base is uridine.

The term "nucleotide sequence complementary to the nucleotide sequence set forth in SEQ ID NO. x" refers to the nucleotide sequence of the complementary strand of a nucleic acid strand having SEQ ID NO. x. The term "complementary strand" is used herein interchangeably with the term "complement". The complement of a nucleic acid strand can be the complement of a coding strand or the complement of a non-coding strand. When referring to double stranded nucleic acids, the complement of a nucleic acid having SEQ ID NO. x refers to the complementary strand of the strand having SEQ ID NO. x or to any nucleic acid having the nucleotide sequence of the complementary strand of SEQ ID NO. x. When referring to a single stranded nucleic acid having the nucleotide sequence SEQ ID NO. x, the complement of this nucleic acid is a nucleic acid having a nucleotide sequence which is complementary to that of SEQ ID NO. x. The nucleotide sequences and complementary sequences thereof are always given in the 5' to 3' direction. The term "complement" and "reverse complement" are used interchangeably herein.

The term "operably linked" is intended to mean that the promoter is associated with the nucleic acid in such a manner as to facilitate transcription of the nucleic acid.

The term "polymorphism" refers to the coexistence of more than one form of a gene or portion thereof. A portion of a gene of which there are at least two different forms, i.e., two different nucleotide sequences, is referred to as a "polymorphic region of a gene". A polymorphic region can be a single nucleotide, the identity of which differs in different alleles. A polymorphic region can also be several nucleotides long.

A "polymorphic gene" refers to a gene having at least one polymorphic region.

To describe a "polymorphic site" in a nucleotide sequence often there is used an "ambiguity code" that stands for the possible variations of nucleotides in one site. The list of ambiguity codes is summarized in the following table:

Ambiguity (IUPAC Nomenclature)	Codes
B	c/g/t
D	a/g/t
H	a/c/t
K	g/t
M	a/c
N	a/c/g/t
R	a/g
S	c/g
V	a/c/g
W	a/t
Y	c/t

So, for example, a "R" in a nucleotide sequence means that either an "a" or a "g" could be at that position.

- 5 The terms "protein", "polypeptide" and "peptide" are used interchangeably herein when referring to a gene product.

10 A "regulatory element", also termed herein "regulatory sequence" is intended to include elements which are capable of modulating transcription from a basic promoter and include elements such as enhancers and silencers. The term "enhancer", also referred to herein as "enhancer element", is intended to include regulatory elements capable of increasing, stimulating, or enhancing transcription from a basic promoter. The term "silencer", also referred to herein as "silencer element" is intended to include regulatory elements capable of decreasing, inhibiting, or repressing transcription from a basic promoter. Regulatory elements are typically present in 5' flanking regions of genes. However, regulatory elements have also been shown to be present in other regions of a gene, in particular in introns. Thus, it is possible that genes have regulatory elements located in introns, exons, coding

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regions, and 3' flanking sequences. Such regulatory elements are also intended to be encompassed by the present invention and can be identified by any of the assays that can be used to identify regulatory elements in 5' flanking regions of genes.

5 The term "regulatory element" further encompasses "tissue specific" regulatory elements, i.e., regulatory elements which effect expression of the selected DNA sequence preferentially in specific cells (e.g., cells of a specific tissue). gene expression occurs preferentially in a specific cell if expression in this cell type is significantly higher than expression in other cell types. The term "regulatory
10 element" also encompasses non-tissue specific regulatory elements, i.e., regulatory elements which are active in most cell types. Furthermore, a regulatory element can be a constitutive regulatory element, i.e., a regulatory element which constitutively regulates transcription, as opposed to a regulatory element which is inducible, i.e., a regulatory element which is active primarily in response to a stimulus. A stimulus
15 can be, e.g., a molecule, such as a hormone, cytokine, heavy metal, phorbol ester, cyclic AMP (cAMP), or retinoic acid.

Regulatory elements are typically bound by proteins, e.g., transcription factors. The term "transcription factor" is intended to include proteins or modified forms thereof,
20 which interact preferentially with specific nucleic acid sequences, i.e., regulatory elements, and which in appropriate conditions stimulate or repress transcription. Some transcription factors are active when they are in the form of a monomer. Alternatively, other transcription factors are active in the form of a dimer consisting of two identical proteins or different proteins (heterodimer). Modified forms of
25 transcription factors are intended to refer to transcription factors having a post-translational modification, such as the attachment of a phosphate group. The activity of a transcription factor is frequently modulated by a post-translational modification. For example, certain transcription factors are active only if they are phosphorylated on specific residues. Alternatively, transcription factors can be active in the absence
30 of phosphorylated residues and become inactivated by phosphorylation. A list of

known transcription factors and their DNA binding site can be found, e.g., in public databases, e.g., TFMATRIX Transcription Factor Binding Site Profile database.

5 As used herein, the term "specifically hybridizes" or "specifically detects" refers to the ability of a nucleic acid molecule of the invention to hybridize to at least approximately 6, 12, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130 or 140 consecutive nucleotides of either strand of a gene.

10 The term "wild-type allele" refers to an allele of a gene which, when present in two copies in a subject results in a wild-type phenotype. There can be several different wild-type alleles of a specific gene, since certain nucleotide changes in a gene may not affect the phenotype of a subject having two copies of the gene with the nucleotide changes.

15 "Adverse drug reaction" (ADR) as used herein refers to an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product. In it's most severe form an ADR might lead to the death of an individual.

20 The term "Drug Response" is intended to mean any response that a patient exhibits upon drug administration. Specifically drug response includes beneficial, i.e. desired drug effects, ADR or no detectable reaction at all. More specifically the term drug response could also have a qualitative meaning, i.e. it embraces low or high
25 beneficial effects, respectively and mild or severe ADR, respectively. The term "Statin Response" as used herein refers to drug response after statin administration. An individual drug response includes also a good or bad metabolizing of the drug, meaning that "bad metabolizers" accumulate the drug in the body and by this could show side effects of the drug due to accumulative overdoses.

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"Candidate gene" as used herein includes genes that can be assigned to either normal cardiovascular function or to metabolic pathways that are related to onset and/or progression of cardiovascular diseases.

5 With regard to drug response the term "candidate gene" includes genes that can be assigned to distinct phenotypes regarding the patient's response to drug administration. Those phenotypes may include patients who benefit from relatively small amounts of a given drug (high responders) or patients who need relatively high doses in order to obtain the same benefit (low responders). In addition those
10 phenotypes may include patients who can tolerate high doses of a medicament without exhibiting ADR, or patients who suffer from ADR even after receiving only low doses of a medicament.

15 As neither the development of cardiovascular diseases nor the patient's response to drug administration is completely understood, the term "candidate gene" may also comprise genes with presently unknown function.

"PA SNP" (phenotype associated SNP) refers to a polymorphic site which shows a significant association with a patients phenotype (healthy, diseased, low or high
20 responder, drug tolerant, ADR prone, etc.)

"PA gene" (phenotype associated gene) refers to a genomic locus harbouring a PA SNP, irrespective of the actual function of this gene locus.

25 PA gene polypeptide refers to a polypeptide encoded at least in part by a PA gene.

The term "Haplotype" as used herein refers to a group of two or more SNPs that are functionally and/or spatially linked. I.e. haplotypes define groups of SNPs that lie inside genes belonging to identical (or related metabolic) pathways and/or lie on the
30 same chromosome. Haplotypes are expected to give better predictive/diagnostic information than a single SNP

The term "statin" is intended to embrace all inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Statins specifically inhibit the enzyme HMG-CoA reductase which catalyzes the rate limiting step in cholesterol biosynthesis. Known statins are Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Pravastatin and Simvastatin.

Methods for Assessing Cardiovascular Status

The present invention provides diagnostic methods for assessing cardiovascular status in a human individual. Cardiovascular status as used herein refers to the physiological status of an individual's cardiovascular system as reflected in one or more markers or indicators. Status markers include without limitation clinical measurements such as, e.g., blood pressure, electrocardiographic profile, and differentiated blood flow analysis as well as measurements of LDL- and HDL-Cholesterol levels, other lipids and other well established clinical parameters that are standard in the art. Status markers according to the invention include diagnoses of one or more cardiovascular syndromes, such as, e.g., hypertension, acute myocardial infarction, silent myocardial infarction, stroke, and atherosclerosis. It will be understood that a diagnosis of a cardiovascular syndrome made by a medical practitioner encompasses clinical measurements and medical judgement. Status markers according to the invention are assessed using conventional methods well known in the art. Also included in the evaluation of cardiovascular status are quantitative or qualitative changes in status markers with time, such as would be used, e.g., in the determination of an individual's response to a particular therapeutic regimen.

The methods are carried out by the steps of:

- 5 (i) determining the sequence of one or more polymorphic positions within one, several or all of the genes listed in Examples or other genes mentioned in this file in the individual to establish a polymorphic pattern for the individual; and
- 10 (ii) comparing the polymorphic pattern established in (i) with the polymorphic patterns of humans exhibiting different markers of cardiovascular status. The polymorphic pattern of the individual is, preferably, highly similar and, most preferably, identical to the polymorphic pattern of individuals who exhibit particular status markers, cardiovascular syndromes, and/or particular patterns of response to therapeutic interventions. Polymorphic patterns may also include polymorphic positions in other genes which are shown, in combination with one or more polymorphic positions in the genes listed in the Examples, to correlate with the presence of particular status markers. In one embodiment, the method involves comparing an individual's polymorphic pattern with polymorphic patterns of individuals who have been shown to respond positively or negatively to a particular therapeutic regimen. Therapeutic regimen as used herein refers to treatments aimed at the elimination or amelioration of symptoms and events associated cardiovascular disease. Such treatments include without limitation one or more of alteration in diet, lifestyle, and exercise regimen; invasive and noninvasive surgical techniques such as atherectomy, angioplasty, and coronary bypass surgery; and pharmaceutical interventions, such as administration of ACE inhibitors, 15 angiotensin II receptor antagonists, diuretics, alpha-adrenoreceptor antagonists, cardiac glycosides, phosphodiesterase inhibitors, beta-adrenoreceptor antagonists, calcium channel blockers, HMG-CoA reductase inhibitors, imidazoline receptor blockers, endothelin receptor blockers, organic nitrites, and modulators of protein function of genes listed in the Examples. Interventions with pharmaceutical agents not yet known whose activity correlates with particular polymorphic patterns associated with 20 25 30

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cardiovascular disease are also encompassed. It is contemplated, for example, that patients who are candidates for a particular therapeutic regimen will be screened for polymorphic patterns that correlate with responsivity to that particular regimen.

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In a preferred embodiment, the method involves comparing an individual's polymorphic pattern with polymorphic patterns of individuals who exhibit or have exhibited one or more markers of cardiovascular disease, such as, e.g., elevated LDL-Cholesterol levels, high blood pressure, abnormal electrocardiographic profile, myocardial infarction, stroke, or atherosclerosis.

10

In another embodiment, the method involves comparing an individual's polymorphic pattern with polymorphic patterns of individuals who exhibit or have exhibited one or more drug related phenotypes, such as, e.g., low or high drug response, or adverse drug reactions.

15

In practicing the methods of the invention, an individual's polymorphic pattern can be established by obtaining DNA from the individual and determining the sequence at predetermined polymorphic positions in the genes such as those described in this file.

20

The DNA may be obtained from any cell source. Non-limiting examples of cell sources available in clinical practice include blood cells, buccal cells, cervicovaginal cells, epithelial cells from urine, fetal cells, or any cells present in tissue obtained by biopsy. Cells may also be obtained from body fluids, including without limitation blood, saliva, sweat, urine, cerebrospinal fluid, feces, and tissue exudates at the site of infection or inflammation. DNA is extracted from the cell source or body fluid using any of the numerous methods that are standard in the art. It will be understood that the particular method used to extract DNA will depend on the nature of the source.

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Diagnostic and Prognostic Assays

The present invention provides methods for determining the molecular structure of at least one polymorphic region of a gene, specific allelic variants of said polymorphic region being associated with cardiovascular disease. In one embodiment, determining the molecular structure of a polymorphic region of a gene comprises determining the identity of the allelic variant. A polymorphic region of a gene, of which specific alleles are associated with cardiovascular disease can be located in an exon, an intron, at an intron/exon border, or in the promoter of the gene.

The invention provides methods for determining whether a subject has, or is at risk, of developing a cardiovascular disease. Such disorders can be associated with an aberrant gene activity, e.g., abnormal binding to a form of a lipid, or an aberrant gene protein level. An aberrant gene protein level can result from an aberrant transcription or post-transcriptional regulation. Thus, allelic differences in specific regions of a gene can result in differences of gene protein due to differences in regulation of expression. In particular, some of the identified polymorphisms in the human gene may be associated with differences in the level of transcription, RNA maturation, splicing, or translation of the gene or transcription product.

In preferred embodiments, the methods of the invention can be characterized as comprising detecting, in a sample of cells from the subject, the presence or absence of a specific allelic variant of one or more polymorphic regions of a gene. The allelic differences can be: (i) a difference in the identity of at least one nucleotide or (ii) a difference in the number of nucleotides, which difference can be a single nucleotide or several nucleotides.

A preferred detection method is allele specific hybridization using probes overlapping the polymorphic site and having about 5, 10, 20, 25, or 30 nucleotides around the polymorphic region. Examples of probes for detecting specific allelic variants of the polymorphic region located in intron X are probes comprising a nucleotide

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sequence set forth in any of SEQ ID NO. X. In a preferred embodiment of the invention, several probes capable of hybridizing specifically to allelic variants are attached to a solid phase support, e.g., a "chip". Oligonucleotides can be bound to a solid support by a variety of processes, including lithography. For example a chip can hold up to 250,000 oligonucleotides (GeneChip, Affymetrix). Mutation detection analysis using these chips comprising oligonucleotides, also termed "DNA probe arrays" is described e.g., in Cronin et al. (1996) Human Mutation 7:244 and in Kozal et al. (1996) Nature Medicine 2:753. In one embodiment, a chip comprises all the allelic variants of at least one polymorphic region of a gene. The solid phase support is then contacted with a test nucleic acid and hybridization to the specific probes is detected. Accordingly, the identity of numerous allelic variants of one or more genes can be identified in a simple hybridization experiment. For example, the identity of the allelic variant of the nucleotide polymorphism of nucleotide A or G at position 33 of Seq ID 1 (baySNP179) and that of other possible polymorphic regions can be determined in a single hybridization experiment.

In other detection methods, it is necessary to first amplify at least a portion of a gene prior to identifying the allelic variant. Amplification can be performed, e.g., by PCR and/or LCR, according to methods known in the art. In one embodiment, genomic DNA of a cell is exposed to two PCR primers and amplification for a number of cycles sufficient to produce the required amount of amplified DNA. In preferred embodiments, the primers are located between 40 and 350 base pairs apart. Preferred primers for amplifying gene fragments of genes of this file are listed in Table 2 in the Examples.

Alternative amplification methods include: self sustained sequence replication (Guatelli, J. C. et al., 1990, Proc. Natl. Acad. Sci. U.S.A. 87:1874-1878), transcriptional amplification system (Kwoh, D. Y. et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:1173-1177), Q-Beta Replicase (Lizardi, P. M. et al., 1988, Bio/Technology 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art.

These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In one embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence at least a portion of a gene and detect allelic variants, e.g., mutations, by comparing the sequence of the sample sequence with the corresponding wild-type (control) sequence. Exemplary sequencing reactions include those based on techniques developed by Maxam and Gilbert (Proc. Natl Acad Sci USA (1977) 74:560) or Sanger (Sanger et al (1977) Proc. Nat. Acad. Sci 74:5463). It is also contemplated that any of a variety of automated sequencing procedures may be utilized when performing the subject assays (Biotechniques (1995) 19:448), including sequencing by mass spectrometry (see, for example, U.S. Pat. No. 5,547,835 and international patent application Publication Number WO 94/16101, entitled DNA Sequencing by Mass Spectrometry by H. Koster; U.S. Pat. No. 5,547,835 and international patent application Publication Number WO 94/21822 entitled "DNA Sequencing by Mass Spectrometry Via Exonuclease Degradation" by H. Koster), and U.S. Pat. No. 5,605,798 and International Patent Application No. PCT/US96/03651 entitled DNA Diagnostics Based on Mass Spectrometry by H. Koster; Cohen et al. (1996) Adv Chromatogr 36:127-162; and Griffin et al. (1993) Appl Biochem Biotechnol 38:147-159). It will be evident to one skilled in the art that, for certain embodiments, the occurrence of only one, two or three of the nucleic acid bases need be determined in the sequencing reaction. For instance, A-track or the like, e.g., where only one nucleotide is detected, can be carried out.

Yet other sequencing methods are disclosed, e.g., in U.S. Pat. No. 5,580,732 entitled "Method of DNA sequencing employing a mixed DNA-polymer chain probe" and U.S. Pat. No. 5,571,676 entitled "Method for mismatch-directed in vitro DNA sequencing".

In some cases, the presence of a specific allele of a gene in DNA from a subject can be shown by restriction enzyme analysis. For example, a specific nucleotide poly-

morphism can result in a nucleotide sequence comprising a restriction site which is absent from the nucleotide sequence of another allelic variant.

5 In other embodiments, alterations in electrophoretic mobility is used to identify the type of gene allelic variant. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita et al. (1989) Proc Natl. Acad. Sci USA 86:2766; see also Cotton (1993) Mutat Res 285:125-144; and Hayashi (1992) Genet Anal Tech Appl 9:73-79). Single-stranded DNA fragments of sample and control nucleic acids
10 are denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more
15 sensitive to a change in sequence. In another preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen et al. (1991) Trends Genet 7:5).

20 In yet another embodiment, the identity of an allelic variant of a polymorphic region is obtained by analyzing the movement of a nucleic acid comprising the polymorphic region in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers et al (1985) Nature 313:495). When DGGE is used as the method of analysis, DNA will be modified to
25 insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing agent gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) Biophys Chem 265:1275).

Examples of techniques for detecting differences of at least one nucleotide between 2 nucleic acids include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide probes may be prepared in which the known polymorphic nucleotide is placed centrally (allele-specific probes) and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki et al. (1986) Nature 324:163); Saiki et al (1989) Proc. Natl Acad. Sci USA 86:6230; and Wallace et al. (1979) Nucl. Acids Res. 6:3543). Such allele specific oligonucleotide hybridization techniques may be used for the simultaneous detection of several nucleotide changes in different polymorphic regions of gene. For example, oligonucleotides having nucleotide sequences of specific allelic variants are attached to a hybridizing membrane and this membrane is then hybridized with labeled sample nucleic acid. Analysis of the hybridization signal will then reveal the identity of the nucleotides of the sample nucleic acid.

Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used. Oligonucleotides used as primers for specific amplification may carry the allelic variant of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs et al (1989) Nucleic Acids Res. 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) Tibtech 11:238; Newton et al. (1989) Nucl. Acids Res. 17:2503). This technique is also termed "PROBE" for Probe Oligo Base Extension. In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini et al (1992) Mol. Cell Probes 6:1).

In another embodiment, identification of the allelic variant is carried out using an oligonucleotide ligation assay (OLA), as described, e.g., in U.S. Pat. No. 4,998,617 and in Landegren, U. et al., Science 241:1077-1080 (1988). The OLA protocol uses two oligonucleotides which are designed to be capable of hybridizing to abutting sequences of a single strand of a target. One of the oligonucleotides is linked to a

separation marker, e.g., biotinylated, and the other is detectably labeled. If the precise complementary sequence is found in a target molecule, the oligonucleotides will hybridize such that their termini abut, and create a ligation substrate. Ligation then permits the labeled oligonucleotide to be recovered using avidin, or another biotin ligand. Nickerson, D. A. et al. have described a nucleic acid detection assay that combines attributes of PCR and OLA (Nickerson, D. A. et al., Proc. Natl. Acad. Sci. (U.S.A.) 87:8923-8927 (1990). In this method, PCR is used to achieve the exponential amplification of target DNA, which is then detected using OLA.

Several techniques based on this OLA method have been developed and can be used to detect specific allelic variants of a polymorphic region of a gene. For example, U.S. Pat. No. 5,593,826 discloses an OLA using an oligonucleotide having 3'-amino group and a 5'-phosphorylated oligonucleotide to form a conjugate having a phosphoramidate linkage. In another variation of OLA described in Tobe et al. ((1996)Nucleic Acids Res 24: 3728), OLA combined with PCR permits typing of two alleles in a single microtiter well. By marking each of the allele-specific primers with a unique hapten, i.e. digoxigenin and fluorescein, each LA reaction can be detected by using hapten specific antibodies that are labeled with different enzyme reporters, alkaline phosphatase or horseradish peroxidase. This system permits the detection of the two alleles using a high throughput format that leads to the production of two different colors.

The invention further provides methods for detecting single nucleotide polymorphisms in a gene. Because single nucleotide polymorphisms constitute sites of variation flanked by regions of invariant sequence, their analysis requires no more than the determination of the identity of the single nucleotide present at the site of variation and it is unnecessary to determine a complete gene sequence for each patient. Several methods have been developed to facilitate the analysis of such single nucleotide polymorphisms.

In one embodiment, the single base polymorphism can be detected by using a specialized exonuclease-resistant nucleotide, as disclosed, e.g., in Mundy, C. R. (U.S. Pat. No. 4,656,127). According to the method, a primer complementary to the allelic sequence immediately 3' to the polymorphic site is permitted to hybridize to a target molecule obtained from a particular animal or human. If the polymorphic site on the target molecule contains a nucleotide that is complementary to the particular exonuclease-resistant nucleotide derivative present, then that derivative will be incorporated onto the end of the hybridized primer. Such incorporation renders the primer resistant to exonuclease, and thereby permits its detection. Since the identity of the exonuclease-resistant derivative of the sample is known, a finding that the primer has become resistant to exonucleases reveals that the nucleotide present in the polymorphic site of the target molecule was complementary to that of the nucleotide derivative used in the reaction. This method has the advantage that it does not require the determination of large amounts of extraneous sequence data.

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In another embodiment of the invention, a solution-based method is used for determining the identity of the nucleotide of a polymorphic site. Cohen, D. et al. (French Patent 2,650,840; PCT Appln. No. WO91/02087). As in the Mundy method of U.S. Pat. No. 4,656,127, a primer is employed that is complementary to allelic sequences immediately 3' to a polymorphic site. The method determines the identity of the nucleotide of that site using labeled dideoxynucleotide derivatives, which, if complementary to the nucleotide of the polymorphic site will become incorporated onto the terminus of the primer.

20

An alternative method, known as Genetic Bit Analysis or GBA™ is described by Goelet, P. et al. (PCT Appln. No. 92/15712). The method of Goelet, P. et al. uses mixtures of labeled terminators and a primer that is complementary to the sequence 3' to a polymorphic site. The labeled terminator that is incorporated is thus determined by, and complementary to, the nucleotide present in the polymorphic site of the target molecule being evaluated. In contrast to the method of Cohen et al. (French Patent 2,650,840; PCT Appln. No. WO91/02087) the method of Goelet, P. et

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al. is preferably a heterogeneous phase assay, in which the primer or the target molecule is immobilized to a solid phase.

5 Recently, several primer-guided nucleotide incorporation procedures for assaying polymorphic sites in DNA have been described (Komher, J. S. et al., Nucl. Acids. Res. 17:7779-7784 (1989); Sokolov, B. P., Nucl. Acids Res. 18:3671 (1990); Syvanen, A. -C., et al., Genomics 8:684-692 (1990), Kuppuswamy, M. N. et al., Proc. Natl. Acad. Sci. (U.S.A.) 88:1143-1147 (1991); Prezant, T. R. et al., Hum. Mutat. 1:159-164 (1992); Ugozzoli, L. et al., GATA 9:107-112 (1992); Nyren, P. et al., Anal. Biochem. 208:171-175 (1993)). These methods differ from GBATM in
10 that they all rely on the incorporation of labeled deoxynucleotides to discriminate between bases at a polymorphic site. In such a format, since the signal is proportional to the number of deoxynucleotides incorporated, polymorphisms that occur in runs of the same nucleotide can result in signals that are proportional to the length of the run
15 (Syvanen, A.-C., et al., Amer. J. Hum. Genet. 52:46-59 (1993)).

For determining the identity of the allelic variant of a polymorphic region located in the coding region of a gene, yet other methods than those described above can be used. For example, identification of an allelic variant which encodes a mutated gene
20 protein can be performed by using an antibody specifically recognizing the mutant protein in, e.g., immunohistochemistry or immunoprecipitation. Antibodies to wild-type gene protein are described, e.g., in Acton et al. (1999) Science 271:518 (anti-mouse gene antibody cross-reactive with human gene). Other antibodies to wild-type gene or mutated forms of gene proteins can be prepared according to methods known
25 in the art. Alternatively, one can also measure an activity of an gene protein, such as binding to a lipid or lipoprotein. Binding assays are known in the art and involve, e.g., obtaining cells from a subject, and performing binding experiments with a labeled lipid, to determine whether binding to the mutated form of the receptor differs from binding to the wild-type of the receptor.

If a polymorphic region is located in an exon, either in a coding or non-coding region of the gene, the identity of the allelic variant can be determined by determining the molecular structure of the mRNA, pre-mRNA, or cDNA. The molecular structure can be determined using any of the above described methods for determining the molecular structure of the genomic DNA, e.g., sequencing and SSCP.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits, such as those described above, comprising at least one probe or primer nucleic acid described herein, which may be conveniently used, e.g., to determine whether a subject has or is at risk of developing a disease associated with a specific gene allelic variant.

Sample nucleic acid for using in the above-described diagnostic and prognostic methods can be obtained from any cell type or tissue of a subject. For example, a subject's bodily fluid (e.g. blood) can be obtained by known techniques (e.g. venipuncture) or from human tissues like heart (biopsies, transplanted organs). Alternatively, nucleic acid tests can be performed on dry samples (e.g. hair or skin). Fetal nucleic acid samples for prenatal diagnostics can be obtained from maternal blood as described in International Patent Application No. WO91/07660 to Bianchi. Alternatively, amniocytes or chorionic villi may be obtained for performing prenatal testing.

Diagnostic procedures may also be performed in situ directly upon tissue sections (fixed and/or frozen) of patient tissue obtained from biopsies or resections, such that no nucleic acid purification is necessary. Nucleic acid reagents may be used as probes and/or primers for such in situ procedures (see, for example, Nuovo, G. J., 1992, PCR in situ hybridization: protocols and applications, Raven Press, New York).

In addition to methods which focus primarily on the detection of one nucleic acid sequence, profiles may also be assessed in such detection schemes. Fingerprint

profiles may be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR.

5 In practicing the present invention, the distribution of polymorphic patterns in a large number of individuals exhibiting particular markers of cardiovascular status or drug response is determined by any of the methods described above, and compared with the distribution of polymorphic patterns in patients that have been matched for age, ethnic origin, and/or any other statistically or medically relevant parameters, who exhibit quantitatively or qualitatively different status markers. Correlations are
10 achieved using any method known in the art, including nominal logistic regression, chi square tests or standard least squares regression analysis. In this manner, it is possible to establish statistically significant correlations between particular polymorphic patterns and particular cardiovascular statuses (given in p values). It is further possible to establish statistically significant correlations between particular
15 polymorphic patterns and changes in cardiovascular status or drug response such as, would result, e.g., from particular treatment regimens. In this manner, it is possible to correlate polymorphic patterns with responsivity to particular treatments.

20 In another embodiment of the present invention two or more polymorphic regions are combined to define so called 'haplotypes'. Haplotypes are groups of two or more SNPs that are functionally and/or spatially linked. It is possible to combine SNPs that are disclosed in the present invention either with each other or with additional polymorphic regions to form a haplotype. Haplotypes are expected to give better predictive/diagnostic information than a single SNP.

25 In a preferred embodiment of the present invention a panel of SNPs/haplotypes is defined that predicts the risk for CVD or drug response. This predictive panel is then used for genotyping of patients on a platform that can genotype multiple SNPs at the same time (Multiplexing). Preferred platforms are e.g. gene chips (Affymetrix) or the
30 Luminex LabMAP reader. The subsequent identification and evaluation of a patient's haplotype can then help to guide specific and individualized therapy.

For example the present invention can identify patients exhibiting genetic polymorphisms or haplotypes which indicate an increased risk for adverse drug reactions. In that case the drug dose should be lowered in a way that the risk for ADR is diminished. Also if the patient's response to drug administration is particularly high (or the patient is badly metabolizing the drug), the drug dose should be lowered to avoid the risk of ADR.

In turn if the patient's response to drug administration is low (or the patient is a particularly high metabolizer of the drug), and there is no evident risk of ADR, the drug dose should be raised to an efficacious level.

It is self evident that the ability to predict a patient's individual drug response should affect the formulation of a drug; i.e. drug formulations should be tailored in a way that they suit the different patient classes (low/high responder, poor/good metabolizer, ADR prone patients). Those different drug formulations may encompass different doses of the drug, i.e. the medicinal products contains low or high amounts of the active substance. In another embodiment of the invention the drug formulation may contain additional substances that facilitate the beneficial effects and/or diminish the risk for ADR (Folkers et al. 1991, US Pat. 5,316,765).

Isolated Polymorphic Nucleic Acids, Probes, and Vectors

The present invention provides isolated nucleic acids comprising the polymorphic positions described herein for human genes; vectors comprising the nucleic acids; and transformed host cells comprising the vectors. The invention also provides probes which are useful for detecting these polymorphisms.

In practicing the present invention, many conventional techniques in molecular biology, microbiology, and recombinant DNA, are used. Such techniques are well known and are explained fully in, for example, Sambrook et al., 1989, Molecular

Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; DNA Cloning: A Practical Approach, Volumes I and II, 1985 (D. N. Glover ed.); Oligonucleotide Synthesis, 1984, (M. L. Gait ed.); Nucleic Acid Hybridization, 1985, (Hames and Higgins); Ausubel et al.,
5 Current Protocols in Molecular Biology, 1997, (John Wiley and Sons); and Methods in Enzymology Vol. 154 and Vol. 155 (Wu and Grossman, and Wu, eds., respectively).

10 Insertion of nucleic acids (typically DNAs) comprising the sequences in a functional surrounding like full length cDNA of the present invention into a vector is easily accomplished when the termini of both the DNAs and the vector comprise compatible restriction sites. If this cannot be done, it may be necessary to modify the termini of the DNAs and/or vector by digesting back single-stranded DNA overhangs
15 generated by restriction endonuclease cleavage to produce blunt ends, or to achieve the same result by filling in the single-stranded termini with an appropriate DNA polymerase.

Alternatively, any site desired may be produced, e.g., by ligating nucleotide sequences (linkers) onto the termini. Such linkers may comprise specific oligo-
20 nucleotide sequences that define desired restriction sites. Restriction sites can also be generated by the use of the polymerase chain reaction (PCR). See, e.g., Saiki et al., 1988, Science 239:48. The cleaved vector and the DNA fragments may also be modified if required by homopolymeric tailing.

25 The nucleic acids may be isolated directly from cells or may be chemically synthesized using known methods. Alternatively, the polymerase chain reaction (PCR) method can be used to produce the nucleic acids of the invention, using either chemically synthesized strands or genomic material as templates. Primers used for PCR can be synthesized using the sequence information provided herein and can
30 further be designed to introduce appropriate new restriction sites, if desirable, to facilitate incorporation into a given vector for recombinant expression.

The nucleic acids of the present invention may be flanked by native gene sequences, or may be associated with heterologous sequences, including promoters, enhancers, response elements, signal sequences, polyadenylation sequences, introns, 5'- and 3'-noncoding regions, and the like. The nucleic acids may also be modified by many means known in the art. Non-limiting examples of such modifications include methylation, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoroamidates, carbamates, morpholines etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.). Nucleic acids may contain one or more additional covalently linked moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), intercalators (e.g., acridine, psoralen, etc.), chelators (e.g., metals, radioactive metals, iron, oxidative metals, etc.), and alkylators. PNAs are also included. The nucleic acid may be derivatized by formation of a methyl or ethyl phosphotriester or an alkyl phosphoramidate linkage. Furthermore, the nucleic acid sequences of the present invention may also be modified with a label capable of providing a detectable signal, either directly or indirectly. Exemplary labels include radioisotopes, fluorescent molecules, biotin, and the like.

The invention also provides nucleic acid vectors comprising the gene sequences or derivatives or fragments thereof of genes described in the Examples. A large number of vectors, including plasmid and fungal vectors, have been described for replication and/or expression in a variety of eukaryotic and prokaryotic hosts, and may be used for gene therapy as well as for simple cloning or protein expression. Non-limiting examples of suitable vectors include without limitation pUC plasmids, pET plasmids (Novagen, Inc., Madison, Wis.), or pRSET or pREP (Invitrogen, San Diego, Calif.), and many appropriate host cells, using methods disclosed or cited herein or otherwise known to those skilled in the relevant art. The particular choice of vector/host is not critical to the practice of the invention.

Suitable host cells may be transformed/transfected/infected as appropriate by any suitable method including electroporation, CaCl_2 mediated DNA uptake, fungal or viral infection, microinjection, microprojectile, or other established methods.

5 Appropriate host cells included bacteria, archebacteria, fungi, especially yeast, and plant and animal cells, especially mammalian cells. A large number of transcription initiation and termination regulatory regions have been isolated and shown to be effective in the transcription and translation of heterologous proteins in the various hosts. Examples of these regions, methods of isolation, manner of manipulation, etc.
10 are known in the art. Under appropriate expression conditions, host cells can be used as a source of recombinantly produced peptides and polypeptides encoded by genes of the Examples. Nucleic acids encoding peptides or polypeptides from gene sequences of the Examples may also be introduced into cells by recombination events. For example, such a sequence can be introduced into a cell and thereby effect
15 homologous recombination at the site of an endogenous gene or a sequence with substantial identity to the gene. Other recombination-based methods such as non-homologous recombinations or deletion of endogenous genes by homologous recombination may also be used.

20 In case of proteins that form heterodimers or other multimers, both or all subunits have to be expressed in one system or cell.

The nucleic acids of the present invention find use as probes for the detection of genetic polymorphisms and as templates for the recombinant production of normal or
25 variant peptides or polypeptides encoded by genes listed in the Examples.

Probes in accordance with the present invention comprise without limitation isolated nucleic acids of about 10-100 bp, preferably 15-75 bp and most preferably 17-25 bp in length, which hybridize at high stringency to one or more of the polymorphic
30 sequences disclosed herein or to a sequence immediately adjacent to a polymorphic position. Furthermore, in some embodiments a full-length gene sequence may be

used as a probe. In one series of embodiments, the probes span the polymorphic positions in genes disclosed herein. In another series of embodiments, the probes correspond to sequences immediately adjacent to the polymorphic positions.

5 Polymorphic Polypeptides and Polymorphism-Specific Antibodies

The present invention encompasses isolated peptides and polypeptides encoded by genes listed in the Examples comprising polymorphic positions disclosed herein. In one preferred embodiment, the peptides and polypeptides are useful screening targets
10 to identify cardiovascular drugs. In another preferred embodiment, the peptides and polypeptides are capable of eliciting antibodies in a suitable host animal that react specifically with a polypeptide comprising the polymorphic position and distinguish it from other polypeptides having a different sequence at that position.

15 Polypeptides according to the invention are preferably at least five or more residues in length, preferably at least fifteen residues. Methods for obtaining these polypeptides are described below. Many conventional techniques in protein biochemistry and immunology are used. Such techniques are well known and are explained in Immunochemical Methods in Cell and Molecular Biology, 1987 (Mayer and Waler,
20 eds; Academic Press, London); Scopes, 1987, Protein Purification: Principles and Practice, Second Edition (Springer-Verlag, N.Y.) and Handbook of Experimental Immunology, 1986, Volumes I-IV (Weir and Blackwell eds.).

25 Nucleic acids comprising protein-coding sequences can be used to direct the ITT recombinant expression of polypeptides encoded by genes disclosed herein in intact cells or in cell-free translation systems. The known genetic code, tailored if desired for more efficient expression in a given host organism, can be used to synthesize oligonucleotides encoding the desired amino acid sequences. The polypeptides may be isolated from human cells, or from heterologous organisms or cells (including, but
30 not limited to, bacteria, fungi, insect, plant, and mammalian cells) into which an

appropriate protein-coding sequence has been introduced and expressed. Furthermore, the polypeptides may be part of recombinant fusion proteins.

Peptides and polypeptides may be chemically synthesized by commercially available automated procedures, including, without limitation, exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. The polypeptides are preferably prepared by solid phase peptide synthesis as described by Merrifield, 1963, J. Am. Chem. Soc. 85:2149.

Methods for polypeptide purification are well-known in the art, including, without limitation, preparative disc-gel electrophoresis, isoelectric focusing, HPLC, reversed-phase HPLC, gel filtration, ion exchange and partition chromatography, and countercurrent distribution. For some purposes, it is preferable to produce the polypeptide in a recombinant system in which the protein contains an additional sequence tag that facilitates purification, such as, but not limited to, a polyhistidine sequence. The polypeptide can then be purified from a crude lysate of the host cell by chromatography on an appropriate solid-phase matrix. Alternatively, antibodies produced against peptides encoded by genes disclosed herein, can be used as purification reagents. Other purification methods are possible.

The present invention also encompasses derivatives and homologues of the polypeptides. For some purposes, nucleic acid sequences encoding the peptides may be altered by substitutions, additions, or deletions that provide for functionally equivalent molecules, i.e., function-conservative variants. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of similar properties, such as, for example, positively charged amino acids (arginine, lysine, and histidine); negatively charged amino acids (aspartate and glutamate); polar neutral amino acids; and non-polar amino acids.

The isolated polypeptides may be modified by, for example, phosphorylation, sulfation, acylation, or other protein modifications. They may also be modified with

a label capable of providing a detectable signal, either directly or indirectly, including, but not limited to, radioisotopes and fluorescent compounds.

The present invention also encompasses antibodies that specifically recognize the polymorphic positions of the invention and distinguish a peptide or polypeptide containing a particular polymorphism from one that contains a different sequence at that position. Such polymorphic position-specific antibodies according to the present invention include polyclonal and monoclonal antibodies. The antibodies may be elicited in an animal host by immunization with peptides encoded by genes disclosed herein or may be formed by in vitro immunization of immune cells. The immunogenic components used to elicit the antibodies may be isolated from human cells or produced in recombinant systems. The antibodies may also be produced in recombinant systems programmed with appropriate antibody-encoding DNA. Alternatively, the antibodies may be constructed by biochemical reconstitution of purified heavy and light chains. The antibodies include hybrid antibodies (i.e., containing two sets of heavy chain/light chain combinations, each of which recognizes a different antigen), chimeric antibodies (i.e., in which either the heavy chains, light chains, or both, are fusion proteins), and univalent antibodies (i.e., comprised of a heavy chain/light chain complex bound to the constant region of a second heavy chain). Also included are Fab fragments, including Fab' and F(ab).sub.2 fragments of antibodies. Methods for the production of all of the above types of antibodies and derivatives are well-known in the art and are discussed in more detail below. For example, techniques for producing and processing polyclonal antisera are disclosed in Mayer and Walker, 1987, Immunochemical Methods in Cell and Molecular Biology, (Academic Press, London). The general methodology for making monoclonal antibodies by hybridomas is well known. Immortal antibody-producing cell lines can be created by cell fusion, and also by other techniques such as direct transformation of B lymphocytes with oncogenic DNA, or transfection with Epstein-Barr virus. See, e.g., Schreier et al., 1980, Hybridoma Techniques; U.S. Pat. Nos. 4,341,761; 4,399,121; 4,427,783; 4,444,887; 4,466,917; 4,472,500; 4,491,632; and 4,493,890. Panels of monoclonal antibodies produced against peptides encoded

by genes disclosed herein can be screened for various properties; i.e. for isotype, epitope affinity, etc.

5 The antibodies of this invention can be purified by standard methods, including but not limited to preparative disc-gel electrophoresis, isoelectric focusing, HPLC, reversed-phase HPLC, gel filtration, ion exchange and partition chromatography, and countercurrent distribution. Purification methods for antibodies are disclosed, e.g., in The Art of Antibody Purification, 1989, Amicon Division, W. R. Grace & Co. General protein purification methods are described in Protein Purification: Principles
10 and Practice, R. K. Scopes, Ed., 1987, Springer-Verlag, New York, N.Y.

Methods for determining the immunogenic capability of the disclosed sequences and the characteristics of the resulting sequence-specific antibodies and immune cells are well-known in the art. For example, antibodies elicited in response to a peptide
15 comprising a particular polymorphic sequence can be tested for their ability to specifically recognize that polymorphic sequence, i.e., to bind differentially to a peptide or polypeptide comprising the polymorphic sequence and thus distinguish it from a similar peptide or polypeptide containing a different sequence at the same position.

20

Kits

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As set forth herein, the invention provides diagnostic methods, e.g., for determining the identity of the allelic variants of polymorphic regions present in the gene loci of genes disclosed herein, wherein specific allelic variants of the polymorphic region are associated with cardiovascular diseases. In a preferred embodiment, the diagnostic kit can be used to determine whether a subject is at risk of developing a cardiovascular disease. This information could then be used, e.g., to optimize treatment of such individuals.

30

In preferred embodiments, the kit comprises a probe or primer which is capable of hybridizing to a gene and thereby identifying whether the gene contains an allelic variant of a polymorphic region which is associated with a risk for cardiovascular disease. The kit preferably further comprises instructions for use in diagnosing a subject as having, or having a predisposition, towards developing a cardiovascular disease. The probe or primers of the kit can be any of the probes or primers described in this file.

Preferred kits for amplifying a region of a gene comprising a polymorphic region of interest comprise one, two or more primers.

Antibody-based diagnostic methods and kits

The invention also provides antibody-based methods for detecting polymorphic patterns in a biological sample. The methods comprise the steps of: (i) contacting a sample with one or more antibody preparations, wherein each of the antibody preparations is specific for a particular polymorphic form of the proteins encoded by genes disclosed herein, under conditions in which a stable antigen-antibody complex can form between the antibody and antigenic components in the sample; and (ii) detecting any antigen-antibody complex formed in step (i) using any suitable means known in the art, wherein the detection of a complex indicates the presence of the particular polymorphic form in the sample.

Typically, immunoassays use either a labelled antibody or a labelled antigenic component (e.g., that competes with the antigen in the sample for binding to the antibody). Suitable labels include without limitation enzyme-based, fluorescent, chemiluminescent, radioactive, or dye molecules. Assays that amplify the signals from the probe are also known, such as, for example, those that utilize biotin and avidin, and enzyme-labelled immunoassays, such as ELISA assays.

The present invention also provides kits suitable for antibody-based diagnostic applications. Diagnostic kits typically include one or more of the following components:

- 5 (i) Polymorphism-specific antibodies. The antibodies may be pre-labelled; alternatively, the antibody may be unlabelled and the ingredients for labelling may be included in the kit in separate containers, or a secondary, labelled antibody is provided; and
- 10 (ii) Reaction components: The kit may also contain other suitably packaged reagents and materials needed for the particular immunoassay protocol, including solid-phase matrices, if applicable, and standards.

The kits referred to above may include instructions for conducting the test.
15 Furthermore, in preferred embodiments, the diagnostic kits are adaptable to high-throughput and/or automated operation.

Drug Targets and Screening Methods

20 According to the present invention, nucleotide sequences derived from genes disclosed herein and peptide sequences encoded by genes disclosed herein, particularly those that contain one or more polymorphic sequences, comprise useful targets to identify cardiovascular drugs, i.e., compounds that are effective in treating one or more clinical symptoms of cardiovascular disease. Furthermore, especially when a
25 protein is a multimeric protein that are build of two or more subunits, is a combination of different polymorphic subunits very useful.

Drug targets include without limitation (i) isolated nucleic acids derived from the genes disclosed herein, and (ii) isolated peptides and polypeptides encoded by genes
30 disclosed herein, each of which comprises one or more polymorphic positions.

In vitro screening methods

5 In one series of embodiments, an isolated nucleic acid comprising one or more polymorphic positions is tested in vitro for its ability to bind test compounds in a sequence-specific manner. The methods comprise:

10 (i) providing a first nucleic acid containing a particular sequence at a polymorphic position and a second nucleic acid whose sequence is identical to that of the first nucleic acid except for a different sequence at the same polymorphic position;

(ii) contacting the nucleic acids with a multiplicity of test compounds under conditions appropriate for binding; and

15 (iii) identifying those compounds that bind selectively to either the first or second nucleic acid sequence.

Selective binding as used herein refers to any measurable difference in any parameter of binding, such as, e.g., binding affinity, binding capacity, etc.

20 In another series of embodiments, an isolated peptide or polypeptide comprising one or more polymorphic positions is tested in vitro for its ability to bind test compounds in a sequence-specific manner. The screening methods involve:

25 (i) providing a first peptide or polypeptide containing a particular sequence at a polymorphic position and a second peptide or polypeptide whose sequence is identical to the first peptide or polypeptide except for a different sequence at the same polymorphic position;

30 (ii) contacting the polypeptides with a multiplicity of test compounds under conditions appropriate for binding; and

- (iii) identifying those compounds that bind selectively to one of the nucleic acid sequences.

5 In preferred embodiments, high-throughput screening protocols are used to survey a large number of test compounds for their ability to bind the genes or peptides disclosed above in a sequence-specific manner.

10 Test compounds are screened from large libraries of synthetic or natural compounds. Numerous means are currently used for random and directed synthesis of saccharide, peptide, and nucleic acid based compounds. Synthetic compound libraries are commercially available from Maybridge Chemical Co. (Trevillet, Cornwall, UK), Comgenex (Princeton, N.J.), Brandon Associates (Merrimack, N.H.), and Microsource (New Milford, Conn.). A rare chemical library is available from Aldrich (Milwaukee, Wis.). Alternatively, libraries of natural compounds in the form of
15 bacterial, fungal, plant and animal extracts are available from e.g. Pan Laboratories (Bothell, Wash.) or MycoSearch (N.C.), or are readily producible. Additionally, natural and synthetically produced libraries and compounds are readily modified through conventional chemical, physical, and biochemical means.

20 **In vivo screening methods**

Intact cells or whole animals expressing polymorphic variants of genes disclosed herein can be used in screening methods to identify candidate cardiovascular drugs.

25 In one series of embodiments, a permanent cell line is established from an individual exhibiting a particular polymorphic pattern. Alternatively, cells (including without limitation mammalian, insect, yeast, or bacterial cells) are programmed to express a gene comprising one or more polymorphic sequences by introduction of appropriate DNA. Identification of candidate compounds can be achieved using any suitable
30 assay, including without limitation (i) assays that measure selective binding of test compounds to particular polymorphic variants of proteins encoded by genes

disclosed herein; (ii) assays that measure the ability of a test compound to modify (i.e., inhibit or enhance) a measurable activity or function of proteins encoded by genes disclosed herein; and (iii) assays that measure the ability of a compound to modify (i.e., inhibit or enhance) the transcriptional activity of sequences derived from the promoter (i.e., regulatory) regions of genes disclosed herein.

In another series of embodiments, transgenic animals are created in which (i) one or more human genes disclosed herein, having different sequences at particular polymorphic positions are stably inserted into the genome of the transgenic animal; and/or (ii) the endogenous genes disclosed herein are inactivated and replaced with human genes disclosed herein, having different sequences at particular polymorphic positions. See, e.g., Coffman, Semin. Nephrol. 17:404, 1997; Esther et al., Lab. Invest. 74:953, 1996; Murakami et al., Blood Press. Suppl. 2:36, 1996. Such animals can be treated with candidate compounds and monitored for one or more clinical markers of cardiovascular status.

The following are intended as non-limiting examples of the invention.

Material and Methods

Genotyping of patient DNA with the PyrosequencingTM Method as described in the patent application WO 9813523:

First a PCR is set up to amplify the flanking regions around a SNP. Therefor 2 ng of genomic DNA (patient sample) are mixed with a primerset (20 – 40 pmol) producing a 75 to 320 bp PCR fragment with 0,3 to 1 U Qiagens Hot Star Taq PolymeraseTM in a total volume of 20 µL. One primer is biotinylated depending on the direction of the sequencing primer. To force the biotinylated primer to be incorporated it is used 0,8 fold.

For primer design, programmes like Oligo 6™ (Molecular Biology Insights) or Primer Select™ (DNASar) are used. PCR setup is performed by a BioRobot 3000™ from Qiagen. PCR takes place in T1 or Tgradient Thermocyclers™ from Biometra.

- 5 The whole PCR reaction is transferred into a PSQ plate™ (Pyrosequencing) and prepared using the Sample Prep Tool™ and SNP Reagent Kit™ from Pyrosequencing according to their instructions.

Preparation of template for Pyrosequencing™:

10

Sample preparation using PSQ 96 Sample Prep Tool:

1. Mount the PSQ 96 Sample Prep Tool Cover onto the PSQ 96 Sample Prep Tool as follows: Place the cover on the desk, retract the 4 attachment rods by separating the handle from the magnetic rod holder, fit the magnetic rods into
15 the holes of the cover plate, push the handle downward until a click is heard. The PSQ 96 Sample Prep Tool is now ready for use.
2. To transfer beads from one plate to another, place the covered tool into the
20 PSQ 96 Plate containing the samples and lower the magnetic rods by separating the handle from the magnetic rod holder. Move the tool up and down a few times then wait for 30-60 seconds. Transfer the beads into a new PSQ 96 plate containing the solution of choice.
- 25 3. Release the beads by lifting the magnetic rod holder, bringing it together with the handle. Move the tool up and down a few times to make sure that the beads are released.

All steps are performed at room temperature unless otherwise stated.

30

Immobilization of PCR product:

Biotinylated PCR products are immobilized on streptavidin-coated Dynabeads™ M-280 Streptavidin. Parallel immobilization of several samples are performed in the PSQ 96 Plate.

5

1. Mix PCR product, 20 µl of a well optimized PCR, with 25 µl 2X BW-buffer II. Add 60-150 µg Dynabeads. It is also possible to add a mix of Dynabeads and 2X BW-buffer II to the PCR product yielding a final BW-buffer II concentration of approximately 1x.

10

2. Incubate at 65°C for 15 min agitation constantly to keep the beads dispersed. For optimal immobilization of fragments longer than 300 bp use 30 min incubation time.

15

Strand separation:

4. For strand separation, use the PSQ 96 Sample Prep Tool to transfer the beads with the immobilized sample to a PSQ 96 Plate containing 50 µl 0.50 M NaOH per well. Release the beads.

20

5. After approximately 1 min, transfer the beads with the immobilized strand to a PSQ 96 Plate containing 99 µl 1x Annealing buffer per well and mix thoroughly.

25

6. Transfer the beads to a PSQ 96 Plate containing 45 µl of a mix of 1x Annealing buffer and 3-15 pmoles sequencing primer per well.

7. Heat at 80°C for 2 minutes in the PSQ 96 Sample Prep Thermoplate and move to room temperature.

30

8. After reaching room temperature, continue with the sequencing reaction.

Sequencing reaction:

1. Choose the method to be used ("SNP Method") and enter relevant information in the PSQ 96 Instrument Control software.
2. Place the cartridge and PSQ 96 Plate in the PSQ 96 Instrument.
3. Start the run.

Genotyping using the ABI 7700/7900 instrument (TaqMan)

SNP genotyping using the TaqMan (Applied Biosystems/Perkin Elmer) was performed according to the manufacturer's instructions. The TaqMan assay is discussed by Lee et al., Nucleic Acids Research 1993, 21: 3761-3766.

Genotyping with a service contractor:

Qiagen Genomics, formerly Rapigene, is a service contractor for genotyping SNPs in patient samples. Their method is based on a primer extension method where two complementary primers are designed for each genotype that are labeled with different tags. Depending on the genotype only one primer will be elongated together with a certain tag. This tag can be detected with mass spectrometry and is a measure for the respective genotype. The method is described in the following patent: "Detection and identification of nucleic acid molecules - using tags which may be detected by non-fluorescent spectrometry or potentiometry" (WO 9727325).

Examples

To exemplify the present invention and its utility baySNP 28 will be used in the following:

5

baySNP 28 is a C to T polymorphism and presumably resides in the gene of the human acidic 82 kDa protein (information taken from table 3). baySNP 28 was genotyped in various patient cohorts using the primers from table 2. As a result the following number of patients carrying different genotypes were found (information combined from tables 3 and 5a):

10

baySNP	Cohort	Total	Genotype 11 "CC"	Genotype 12 "CT"	Genotype 22 "TT"
28	HELD_FEM_HIRES	12	1	2	9
28	HELD_FEM_LORES	22	3	12	7

When comparing the number of female patients exhibiting a high response to statin therapy (HELD_FEM_HIRES) with the control cohort (HELD_FEM_LORES) it appears that the number of low responders carrying the CT genotype is increased. This points to a lower statin response among female individuals with the CT genotype. Applying statistical tests on those findings the following p-values were obtained (data taken from table 5b):

15

BAYSNP	COMPARISON	GTYPE CPVAL	GTYPE XPVAL	GTYPE LRPVAL
28	HELD_FEM_EFF	0,0506	0,0508	0,0442

20

As at least one of the GTYPE p values is below 0,05 the association of genotype and statin response phenotype is regarded as statistically significant. I.e. the analysis of a patient's genotype can predict the response to statin therapy. In more detail one can calculate the relative risk to exhibit a certain statin response phenotype when carrying a certain genotype (data taken from table 6a):

25

BAYSNP	COMPARISON	GTYPE1	GTYPE2	GTYPE3	RR1	RR2	RR3
28	HELD_FEM_EFF	CC	CT	TT	0,68	0,29	3,38

In case of baySNP 28 the risk to exhibit a high responder phenotype is 3,38 times higher when carrying the TT genotype. This indicates that a TT polymorphism in baySNP 28 is an independent risk factor for high statin response in females. On the other hand carriers of a CT or CC genotype have a reduced risk of being a high responder.

In addition statistical associations can be calculated on the basis on alleles. This calculation would identify risk alleles instead of risk genotypes.

In case of baySNP 28 the following allele counts were obtained (data combined from tables 3 and 5a):

baySNP	Cohort	Total	Allele 1 "C"	Allele 2 "T"
28	HELD_FEM_HIRES	12	4	20
28	HELD_FEM_LORES	22	18	26

When comparing the number of female patients with high statin response (HELD_FEM_HIRES) with the control cohort (HELD_FEM_LORES) it appears that the number of high responders carrying the T allele is increased, whereas the number of high responders carrying the C allele is diminished. This points to a higher statin response among female individuals with the T allele. Applying statistical tests on those findings the following p-values were obtained (data taken from table 5b):

BAYSNP	COMPARISON	ALLELE CPVAL	ALLELE XPVAL	ALLELE LRPVAL
28	HELD_FEM_EFF	0,0411	0,0579	0,0349

As at least one of the ALLELE p values is below 0,05 the association of allele and statin response phenotype is regarded as statistically significant (in this example significant p values were obtained from two statistical tests). I.e. also the analysis of a patient's alleles from baySNP 28 can predict the extend of statin response. In more detail one can calculate the relative risk to exhibit a certain statin response phenotype when carrying a certain allele (data taken from table 6b):

baySNP	Allele 1	Allele 2	COMPARISON	RR1	RR2
28	C	T	HELD_FEM_EFF	0,42	2,39

In case of baySNP 28 the risk to exhibit a high responder phenotype is 2,39 times higher when carrying the T allele. This indicates that the T allele of baySNP28 is an independent risk factor for a high statin response in females. In other words those patients should receive lower doses of statins in order to avoid ADR. However due to their 'high responder' phenotype they will still benefit from the drug. In turn carriers of the C allele should receive higher drug doses in order to experience a beneficial therapeutic effect.

Another example is baySNP 29, which is taken to exemplify polymorphisms relevant for adverse drug reactions. baySNP 29 was found significant when comparing male patients with severe ADR to the respective controls (as defined in table 1b).

The relative risk ratios for the genotypes AA, AG and GG were as follows (data taken from table 6a):

BAYSNP	COMPARISON	GTYPE1	GTYPE2	GTYPE3	RR1	RR2	RR3
29	HELD_MAL_ADRSULN	AA	AG	GG	3,15	0,66	0,32

In this case male patients carrying the AA genotype have a 3,15 times higher risk to suffer from ADR. In other words those patients should either receive lower doses of statins or switch to an alternative therapy in order to avoid ADR. On the other hand

male patients with AG or GG genotypes appear to be more resistant to ADR and hence better tolerate statin therapy.

As can be seen from the following tables some of the associations that are disclosed in the present invention are indicative for more than one phenotype. baySNP 1837 is for example linked to ADR, but also to the risk to suffer from CVD (table 6).

Table 1a Definition of "good" and "bad" serum lipid levels

	"Good"	"Bad"
LDL-Cholesterol [mg/dL]	125 -150	170 - 200
Cholesterol [mg/dL]	190 - 240	265 - 315
HDL-Cholesterol [mg/dL]	60 -105	30 - 55
Triglycerides [mg/dL]	45 - 115	170 - 450

According to the PROCAM algorithm (Assmann, G., Schulte, H. von Eckardstein, A; Am J. Cardiol 77 (1996); 1179-1184) it is possible to define other cohorts. For example a lipid-based equation would calculate y as follows:

$$y = -0.0146 * \text{LDL} + 0.0418 * \text{HDL} - 0.3362 * \ln(\text{TRIGLY})$$

Good or bad cohorts could then be defined in the following way (FEM = female, MAL = male):

FEM_GOOD $y \geq -1.4$

FEM_BAD $y < -1.4$

MAL_GOOD $y \geq -1.7$

MAL_BAD $y < -1.7$

Table 1b Definition of drug response phenotypes

Low responder	Decrease of serum LDL of at least 10% and at most 50% upon administration of 0.8 mg Cerivastatin (female patients)
High responder	Decrease of serum LDL of at least 50% upon administration of 0.4 mg Cerivastatin (female patients)
Very low responder	Decrease of serum LDL of at least 10% and at most 35% upon administration of 0.8 mg Cerivastatin (female patients)
Very high responder	Decrease of serum LDL of at least 55% upon administration of 0.4 mg Cerivastatin (female patients)
Ultra low responder	Decrease of serum LDL of at least 10% and at most 25% upon administration of 0.8 mg Cerivastatin (female patients)
Ultra high responder	Decrease of serum LDL of at least 60% upon administration of 0.4 mg Cerivastatin (female patients)
Tolerant patient	No diagnosis of muscle cramps, muscle pain, muscle weakness, myalgia or myopathy AND serum CK levels below 70 mg/dl in women and below 80 mg/dl in men.
ADR patient (CK increase at least 2×ULN)	Diagnosis of muscle cramps, muscle pain, muscle weakness, myalgia or myopathy OR serum CK levels higher than 140 mg/dl in women and 160 mg/dl in men.
Advanced ADR patient [ADR3] (advanced CK increase, at least 3×ULN)*	Serum CK levels higher than 210 mg/dl in women and 240 mg/dl in men
Severe ADR patient [ADR5] (severe CK increase, at least 5×ULN)*	Serum CK levels higher than 350 mg/dl in women and 400 mg/dl in men

*: When assembling the cohorts for advanced and severe ADR we focused on the CK serum levels as those provide a more independent measure of statin related ADR.

Table 1c Definition of "high" and "low" serum HDL cholesterol levels

	Male individuals	Female individuals
,High' HDL-Cholesterol [mg/dL]	≥ 80	≥ 104
,Low' HDL-Cholesterol [mg/dL]	≤ 35	≤ 37

An informed consent was signed by the patients and control people. Blood was taken
by a physician according to medical standard procedures.

Samples were collected anonymous and labeled with a patient number.

DNA was extracted using kits from Qiagen.

Table 2a Oligonucleotide primers used for genotyping using mass spectrometry

The baySNP number refers to an internal numbering of the PA SNPs. Primer sequences are listed for preamplification of the genomic fragments (primers EF and ER) and for subsequent allele specific PCR of the SNP.

baySNP	SNP	Name	Sequence
28	C137T	CF	gggacggtcggtagatTCTAGAATTGTGCTTCCC
28	C137T	EF	TGTCCAGTGTTAGGAAAA
28	C137T	ER	GACGATGCCTTCAGCACAGATGTGGCTTCTGTATGAG
28	C137T	TF	gctggctcggtcaagaTCTAGAATTGTGCTTCCT
29	A464G	AF	gggacggtcggtagatCATCGGTCAGTGTCCTCCA
29	A464G	EF	GATGTCTGTCTCCTTGATGT
29	A464G	ER	GACGATGCCTTCAGCACAATGTGGGGGTTTTATTTT
29	A464G	GF	gctggctcggtcaagaCATCGGTCAGTGTCCTCCG
52	C397G	CR	gggacggtcggtagatTATTTTATAATGCAAAAG
52	C397G	EF	GACGATGCCTTCAGCACAGTGAATTGCCAGATTAGTG
52	C397G	ER	TCTAAAGTGCTGGGATTG
52	C397G	GR	gctggctcggtcaagaTATTTTATAATGCAAAAC

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baySNP	SNP	Name	Sequenc
56	A429G	AF	gggacggtcggttagatAAGGTCTTTGTACGTGTA
56	A429G	EF	CCAGGTACTGCCTTACAAA
56	A429G	ER	GACGATGCCTTCAGCACAGCTCCCAAATAAATCACTC
56	A429G	GF	gctggctcggtcaagaAAGGTCTTTGTACGTGTG
89	A159G	AR	gggacggtcggttagatTGGAGTCGGGGGAGTCAT
89	A159G	EF	GACGATGCCTTCAGCACATAGTTCAAGGGTAAAGGA
89	A159G	ER	GAGGACGAGATGTAAGAG
89	A159G	GR	gctggctcggtcaagaTGGAGTCGGGGGAGTCAC
90	C154T	CF	gggacggtcggttagatCAGCGCATCCTGAACCAC
90	C154T	EF	GCTGGAACGAGTTCATCCT
90	C154T	ER	GACGATGCCTTCAGCACAGGACCCACCTTCTTGT
90	C154T	TF	gctggctcggtcaagaCAGCGCATCCTGAACCAT
99	C58T	CR	gggacggtcggttagatTCCTGCTCTTTTCTCTAG
99	C58T	EF	GACGATGCCTTCAGCACACACTGACTGCTTACTCTACC
99	C58T	ER	TACTGTGTCTCAGCTCCA
99	C58T	TR	gctggctcggtcaagaTCCTGCTCTTTTCTCTAA
140	C468T	CR	gggacggtcggttagatGTGAATCCCAATACGAAG
140	C468T	EF	GACGATGCCTTCAGCACATAAAAAATAACCAGGTACTCCA
140	C468T	ER	GATGAGTCCTTCACCAAACATACA
140	C468T	TR	gctggctcggtcaagaGTGAATCCCAATACGAAA
152	A587G	AF	gggacggtcggttagatGGTGGGAGGTTCCAGCCA
152	A587G	EF	GCAGGAAGAAAGCTAGAA
152	A587G	ER	GACGATGCCTTCAGCACAAGGCAGGATAATGACAAC
152	A587G	GF	gctggctcggtcaagaGGTGGGAGGTTCCAGCCG
214	A209G	AF	gggacggtcggttagatCATTTCCACCTCACCAA
214	A209G	EF	AGGTATTCCCGGCGTTTC
214	A209G	ER	GACGATGCCTTCAGCACATGTTGTGCGTCTGCTTCC
214	A209G	GF	gctggctcggtcaagaCATTTCCACCTCACCAAG
221	C339G	CF	gggacggtcggttagatTGTGAAGAACTGTTGCTC
221	C339G	EF	CTGAAGCTCATCTGCCTTCT
221	C339G	ER	GACGATGCCTTCAGCACATCCCCTTCTTCTTACCT
221	C339G	GF	gctggctcggtcaagaTGTGAAGAACTGTTGCTG
224	C189T	CR	gggacggtcggttagatGCCCGCTTTTCTTCATCG
224	C189T	EF	GACGATGCCTTCAGCACACTGTCTTCAAGGGCTTACAC

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baySNP	SNP	Name	Sequence
224	C189T	ER	TCCAACCTTCAGGCAAAAC
224	C189T	TR	gctggctcggtagatGCCCGCTTTTCTTCATCA
294	C465T	CR	gggacggtagatCCCAAGGCCAACAGGGAG
294	C465T	EF	GACGATGCCTTCAGCACAGCATTCTTATGCCAGTGTTT
294	C465T	ER	ATCCATCCCATCCTGTGT
294	C465T	TR	gctggctcggtagatGAGTGGGTGCTGTTCCCG
307	C215T	CR	gggacggtagatGAGTGGGTGCTGTTCCCG
307	C215T	EF	GACGATGCCTTCAGCACAGTACTGCCTCTCTGACC
307	C215T	ER	AGTGTGACCTGCTCTCTT
307	C215T	TR	gctggctcggtagatGAGTGGGTGCTGTTCCCA
411	A369T	ER	gacgatgccttcagcacaAACACATTCCCCCTCTAC
411	A369T	EF	GTCTCTATTCCAAGCCAAG
411	A369T	AF	gggacggtagatCCCGCTCCAGCTCCTCA
411	A369T	TF	gctggctcggtagatCCCGCTCCAGCTCCTCT
449	C323G	CR	gggacggtagatCCGCTTCTGCTTCTGCTG
449	C323G	EF	GACGATGCCTTCAGCACAAAGGAGAAGAGGGAGGAGA
449	C323G	ER	GGAGCACGTAAGGAGAAA
449	C323G	GR	gctggctcggtagatCCGCTTCTGCTTCTGCTC
466	C123T	CF	gggacggtagatGGCCAGGGGCTGGAGGGC
466	C123T	EF	TCTTCAGTTCTCTCAGCTTC
466	C123T	ER	GACGATGCCTTCAGCACATCACTAGGGGCTCTTACC
466	C123T	TF	gctggctcggtagatGGCCAGGGGCTGGAGGGT
472	A497G	AR	gggacggtagatTCCTCCCGCTGCTTCAGT
472	A497G	EF	GACGATGCCTTCAGCACATCACTTACCCATCATACTTCTTTTTC
472	A497G	ER	AATCCTGCCTCCACCTT
472	A497G	GR	gctggctcggtagatTCCTCCCGCTGCTTCAGC
542	A402G	AR	gggacggtagatAGAAATTCCTCCCAACT
542	A402G	EF	GACGATGCCTTCAGCACATGATTGAGCCAGTTGTTT
542	A402G	ER	GGGGTGATTTTGAGAGTG
542	A402G	GR	gctggctcggtagatAGAAATTCCTCCCAACC
739	C87G	CR	gggacggtagatGCTGGTTTGACTGGACGG
739	C87G	EF	GACGATGCCTTCAGCACAACTTGGTATAATCCTTTCC
739	C87G	ER	AGGCAACCTAATCCAATT
739	C87G	GR	gctggctcggtagatGCTGGTTTGACTGGACGC

baySNP	SNP	Name	Sequenc
821	A140C	AF	gggacggtcggtagatAGTGCTGTGATACCTGGA
821	A140C	CF	gctggctcggtcaagaAGTGCTGTGATACCTGGC
821	A140C	EF	ACACCCACAAAACAAGAA
821	A140C	ER	GACGATGCCTTCAGCACAGGAACAAGGACATAAAAGAG
1005	A257G	AR	gggacggtcggtagatAGGAAATGTTAGCCCTGT
1005	A257G	EF	GACGATGCCTTCAGCACACTCCACTTCTCTATGCCTC
1005	A257G	ER	GTCCCCAGCTATGTATTGT
1005	A257G	GR	gctggctcggtcaagaAGGAAATGTTAGCCCTGC
1055	A287T	AF	gggacggtcggtagatCTCAGGGAGGGAGAGAGA
1055	A287T	EF	GGGACAGACAGACAGACA
1055	A287T	ER	GACGATGCCTTCAGCACACAACCTCCTTCTTCAGCAC
1055	A287T	TF	gctggctcggtcaagaCTCAGGGAGGGAGAGAGT
1056	A354G	AR	gggacggtcggtagatGCGGCTGCCCCGTCCTGT
1056	A354G	EF	GACGATGCCTTCAGCACAGTGTGTCTATGTGTCTGTGTG
1056	A354G	ER	CGGACTTCTCCTTCTTGT
1056	A354G	GR	gctggctcggtcaagaGCGGCTGCCCCGTCCTGC
1085	A251G	EF	TAGGGTAAGCAGCAAGAG
1085	A251G	ER	CACAAGGCAAGAGATAACA
1085	A251G	AF	gggacggtcggtagatCAGGCAAGATAGACAGCA
1085	A251G	GF	gctggctcggtcaagaCAGGCAAGATAGACAGCG
1086	A104G	EF	GTGCCCATACGAACAGAATAG
1086	A104G	ER	TGCCAAGTACCCCAAGAG
1086	A104G	AR	gggacggtcggtagatCCATTCTCTCCCAGACAT
1086	A104G	GR	gctggctcggtcaagaCCATTCTCTCCCAGACAC
1092	C1687G	CF	gggacggtcggtagatCGTGCGAGCAGCGAAAGC
1092	C1687G	EF	CCAGAGAGAAGTCGAGGAAGAGA
1092	C1687G	ER	GACGATGCCTTCAGCACAGTCACCCCCAAAAGCAGG
1092	C1687G	GF	gctggctcggtcaagaCGTGCGAGCAGCGAAAGG
1096	G454T	EF	GACGATGCCTTCAGCACACTTTTCCTCCTAGCCCAC
1096	G454T	ER	AAGTGATGTAACCCTCCTCTC
1096	G454T	GR	gggacggtcggtagatTCAGCTATAAATAGGGCC
1096	G454T	TR	gctggctcggtcaagaTCAGCTATAAATAGGGCA
1101	C249T	CR	gggacggtcggtagatTGATGGCGGGTGCCAAGG
1101	C249T	EF	GACGATGCCTTCAGCACAGCTCTTTCCTTTGCTTCC

baySNP	SNP	Nam	Sequ nce
1101	C249T	ER	CACTGGGGGTCTCTTAC
1101	C249T	TR	gctggctcggtcaagaTGATGGCGGGTGCCAAGA
1204	A307G	AR	gggacggtcggtagatCAAGGGCACTCACATTAT
1204	A307G	EF	GACGATGCCTTCAGCACAGCTCTTGCGTCTGTTTCC
1204	A307G	ER	TTTCCCTTCTGTCCCCTT
1204	A307G	GR	gctggctcggtcaagaCAAGGGCACTCACATTAC
1504	C180T	CF	gggacggtcggtagatGTGACTTTTGGTTCCAC
1504	C180T	EF	AACTCGGGGTCACTGGTCT
1504	C180T	ER	GACGATGCCTTCAGCACACAGCGGGTATGGAGGATG
1504	C180T	TF	gctggctcggtcaagaGTGACTTTTGGTTCCCAT
1511	G153T	EF	ACACCAGTTCTCCCTCCT
1511	G153T	ER	GACGATGCCTTCAGCACACCCACCTTTCTAATCCT
1511	G153T	GF	gggacggtcggtagatTTGGGACTCTGCGTCAAG
1511	G153T	TF	gctggctcggtcaagaTTGGGACTCTGCGTCAAT
1524	A284C	AF	gggacggtcggtagatCTCTCAAAGCCCACACAA
1524	A284C	CF	gctggctcggtcaagaCTCTCAAAGCCCACACAC
1524	A284C	EF	AGAAAAAGAAAAGGAAAAAGA
1524	A284C	ER	GACGATGCCTTCAGCACAGGAAAGTTACAAGGCTATGA
1556	C367G	CR	gggacggtcggtagatACCTGCCTCTAAGGTCTG
1556	C367G	EF	GACGATGCCTTCAGCACAAAGGAGAAGACAGTTCAAGG
1556	C367G	ER	ACAGTTGCCAGAGAAAAG
1556	C367G	GR	gctggctcggtcaagaACCTGCCTCTAAGGTCTC
1561	A251C	EF	TCACTTGCCTCTACTCCA
1561	A251C	ER	ATACCAGAAAGACTAAGCTCC
1561	A251C	AF	gggacggtcggtagatGGGTGAGCTCTGTGGGCA
1561	A251C	CF	gctggctcggtcaagaGGGTGAGCTCTGTGGGCC
1582	C389T	CR	gggacggtcggtagatCCAAGGGTTATGGCAGGG
1582	C389T	EF	GACGATGCCTTCAGCACACCTGACTATTTGGGGTTGTG
1582	C389T	ER	ATCGCTCTCTGCTTCTGCT
1582	C389T	TR	gctggctcggtcaagaCCAAGGGTTATGGCAGGA
1638	A443G	AR	gggacggtcggtagatCCAAAACCCAGCGCTGT
1638	A443G	EF	GACGATGCCTTCAGCACACTCTTTATCCTGCTTATGGT
1638	A443G	ER	CCAAGCTCACTCTGTAGG
1638	A443G	GR	gctggctcggtcaagaCCAAAACCCAGCGCTGC

baySNP	SNP	Name	S quence
1662	C251T	EF	AATACAATGGAAGCCAAG
1662	C251T	ER	CCTAATCGAACAGAAAGG
1662	C251T	CF	gggacggtcggtagatCCAGTCTCCATCCACTTC
1662	C251T	TF	gctggctcggtcaagaCCAGTCTCCATCCACTTT
1714	A376G	AF	gggacggtcggtagatTGAACGGCATGACGGGGA
1714	A376G	EF	AAGTGTTTCTGCTGTGCCT
1714	A376G	ER	GACGATGCCTTCAGCACACAAGTCCTGGTTTTCCATC
1714	A376G	GF	gctggctcggtcaagaTGAACGGCATGACGGGGG
1722	C89T	CF	gggacggtcggtagatACCCCAGGATGCCACAC
1722	C89T	EF	GTTTATCCTCCTCATGTCC
1722	C89T	ER	GACGATGCCTTCAGCACAGTTACCTTTTCCACCTCTC
1722	C89T	TF	gctggctcggtcaagaACCCCAGGATGCCACAT
1757	A210G	AF	gggacggtcggtagatGGAAACAAACCAAATGA
1757	A210G	EF	CCAGCACCCAAAATAAGA
1757	A210G	ER	GACGATGCCTTCAGCACATAAGTTGAAGCCCTCCC
1757	A210G	GF	gctggctcggtcaagaGGAAACAAACCAAATGG
1765	A240G	AF	gggacggtcggtagatGGCTTCACGGAGGAAGAA
1765	A240G	EF	TTAGGAGCTGTGAGGTATG
1765	A240G	ER	GACGATGCCTTCAGCACATAAGATGGAGCAGGGTAG
1765	A240G	GF	gctggctcggtcaagaGGCTTCACGGAGGAAGAG
1776	A200G	AF	gggacggtcggtagatAAAGGGCTCCCAACACCA
1776	A200G	EF	TGAGCACAAGATCAGAGAGG
1776	A200G	ER	GACGATGCCTTCAGCACAAAGACAGAGACGCAGGAATG
1776	A200G	GF	gctggctcggtcaagaAAAGGGCTCCCAACACCG
1799	C370T	CF	gggacggtcggtagatAGGGACAACCAAAGTGAC
1799	C370T	EF	ATCATCAGAACAGCCCTAC
1799	C370T	ER	GACGATGCCTTCAGCACACAAGCCCACCTACTTACTC
1799	C370T	TF	gctggctcggtcaagaAGGGACAACCAAAGTGAT
1806	A201G	AF	gggacggtcggtagatTGGGCGTCCTGGTGGGCA
1806	A201G	EF	TCTTCGGGCTAACTCTTT
1806	A201G	ER	GACGATGCCTTCAGCACACTGTCACTCCAAACCTTCT
1806	A201G	GF	gctggctcggtcaagaTGGGCGTCCTGGTGGGCG
1837	C413T	CF	gggacggtcggtagatCTCAGCTTCATGCAGGGC
1837	C413T	EF	CCCACTCAGCCCTGCTCTT

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baySNP	SNP	Name	Sequence
1837	C413T	ER	GACGATGCCTTCAGCACAGCATCCTTGGCGGTCTTG
1837	C413T	TF	gctggctcggtcaagaCTCAGCTTCATGCAGGGT
1870	C323T	CF	gggacggtcggtagatCTCCTCATTGCCTCCTTC
1870	C323T	EF	CACCTCTTTTCTCCTTCTCTT
1870	C323T	ER	GACGATGCCTTCAGCACACCCACCCCTCTATCTAC
1870	C323T	TF	gctggctcggtcaagaCTCCTCATTGCCTCCTTT
1882	C115T	CR	gggacggtcggtagatGTCCCCACAAGTCCTCG
1882	C115T	EF	GACGATGCCTTCAGCACAGACCTGTACCCTTTACCC
1882	C115T	ER	TGTTTCCCTGTCTGTTTC
1882	C115T	TR	gctggctcggtcaagaGTCCCCACAAGTCCTCA
1988	C214T	CF	gggacggtcggtagatGTGACTCGGTCTTATACC
1988	C214T	EF	GTGGGCTGTGATTGTGTT
1988	C214T	ER	GACGATGCCTTCAGCACATCTCGTCGTCGTAGTAGTTGT
1988	C214T	TF	gctggctcggtcaagaGTGACTCGGTCTTATACT
2000	C349T	CR	gggacggtcggtagatAGTATGGTAATTAGGAAG
2000	C349T	EF	GACGATGCCTTCAGCACACTGACACTGAGCCACAAC
2000	C349T	ER	AACTGATGAGCAAGAAGGA
2000	C349T	TR	gctggctcggtcaagaAGTATGGTAATTAGGAAA
2071	A338G	AR	gggacggtccgtagatAAAATTGTTTCCTGTGAT
2071	A338G	EF	GACGATGCCTTCAGCACACATTGCTATTCTCAGGCTATA
2071	A338G	ER	CCCATTCTCTGCTTGACAGT
2071	A338G	GR	gctggctcggtcaagaAAAATTGTTTCCTGTGAC
2078	G876T	EF	CCAGAGAGGGGATAAAGA
2078	G876T	ER	GACGATGCCTTCAGCACAGAGTGTCAAGAGGAACAGG
2078	G876T	GF	gggacggtcggtagatTGGCTGCTGAGGTCTGAG
2078	G876T	TF	gctggctcggtcaagaTGGCTGCTGAGGTCTGAT
2085	G415T	EF	GCTTTTCTTTTCATTACATC
2085	G415T	ER	GACGATGCCTTCAGCACACCTCTTTTAGAATCAGAGACA
2085	G415T	GF	gggacggtcggtagatGGTAGTGTTACCAGAAAG
2085	G415T	TF	gctggctcggtcaagaGGTAGTGTTACCAGAAAT
2095	A406G	AR	gggacggtcggtagatTGTGCACCGGGATATTTT
2095	A406G	EF	GACGATGCCTTCAGCACAAATGTGTGCTTGGGTCTT
2095	A406G	ER	GGTGTCTCTCCTCTCTCT
2095	A406G	GR	gctggctcggtcaagaTGTGCACCGGGATATTTT

baySNP	SNP	Nam	Sequenc
2119	A67G	AR	gggacggtcggtagatGTGGGCACCAAACGCTAT
2119	A67G	EF	GACGATGCCTTCAGCACAGATGTAGGGCTGGAAGTG
2119	A67G	ER	TCAAGAAAAATGGGAGTTG
2119	A67G	GR	gctggctcggtcaagaGTGGGCACCAAACGCTAC
2141	A176G	EF	TGTAGCATCGGTAGGTTC
2141	A176G	ER	CAACATCAGACTTTCTTTTTC
2141	A176G	AR	gggacggtcggtagatTGGTACAGGGCTAGTTTT
2141	A176G	GR	gctggctcggtcaagaTGGTACAGGGCTAGTTTC
2182	A318G	AF	gggacggtcggtagatAGGCGGGCCAAGGGTGAA
2182	A318G	EF	TTCTCTCTCCCTTCTGT
2182	A318G	ER	GACGATGCCTTCAGCACATAAATGTTCACTCTTCTTGCT
2182	A318G	GF	gctggctcggtcaagaAGGCGGGCCAAGGGTGAG
2234	G296T	EF	GGGTTGTTCCAGGGCGCTATT
2234	G296T	ER	GACGATGCCTTCAGCACATGTGGAGAGGCCGGGTGC
2234	G296T	GF	gggacggtcggtagatGAACCAGCCCCCTGGAAG
2234	G296T	TF	gctggctcggtcaagaGAACCAGCCCCCTGGAAT
2281	A227C	AR	gggacggtcggtagatCAGGCTTGGAGACCTGGT
2281	A227C	CR	gctggctcggtcaagaCAGGCTTGGAGACCTGGG
2281	A227C	EF	GACGATGCCTTCAGCACAGGGTATTGAGTTGGAAGG
2281	A227C	ER	AAGGCAAGTTCTTAGTTG
2298	A77C	AR	gggacggtcggtagatTCTAAAAGCACTTGAAAT
2298	A77C	CR	gctggctcggtcaagaTCTAAAAGCACTTGAAAG
2298	A77C	EF	GACGATGCCTTCAGCACACCTGCTAGTGTTTTCTGG
2298	A77C	ER	TGTAAGTATAGGTGGTGG
2341	C286T	CR	gggacggtcggtagatTGAAGATTCTGCTCAGCG
2341	C286T	EF	GACGATGCCTTCAGCACAAAGGGCCCGGGACTCAT
2341	C286T	ER	TTTGGGGTCCTGCGGATG
2341	C286T	TR	gctggctcggtcaagaTGAAGATTCTGCTCAGCA
2357	A165G	AF	gggacggtcggtagatCAAAGAAGACGAAAATGA
2357	A165G	EF	CTCAAGTTTGTTACTGATTTCTC
2357	A165G	ER	GACGATGCCTTCAGCACAGGGTACGTCTGCTCTTC
2357	A165G	GF	gctggctcggtcaagaCAAAGAAGACGAAAATGG
2366	G50T	EF	GACGATGCCTTCAGCACACTGCTCCGAAACACGGTC
2366	G50T	ER	GCATCTTCAGCCCTTCTTACTCT

baySNP	SNP	Name	Sequence
2366	G50T	GR	gggacggtcggtagatCTCCTGGGCACCACGGGC
2366	G50T	TR	gctggctcggtcaagaCTCCTGGGCACCACGGGA
2995	A299C	ER	gacgatgccttcagcacaTGGGATTAGACACGAGAG
2995	A299C	EF	AAAGAACTGGAAGAAGGAA
2995	A299C	AF	gggacggtcggtagatGTCACCTCCTTTCCACTA
2995	A299C	CF	gctggctcggtcaagaGTCACCTCCTTTCCACTC
3360	G777T	ER	gacgatgccttcagcacaAGAAAAATGAGAGGGAAAAAC
3360	G777T	EF	GATGAAGGGAAATGGAAC
3360	G777T	GF	gggacggtcggtagatCCAACTATATAGGAGCCG
3360	G777T	TF	gctggctcggtcaagaCCAACTATATAGGAGCCT
3464	A110G	EF	CTGAACCGAGGAGATTTTT
3464	A110G	ER	TGATGCTTACAGAACTGGG
3464	A110G	AF	gggacggtcggtagatGTGTAGTGGGCAGGGTTA
3464	A110G	GF	gctggctcggtcaagaGTGTAGTGGGCAGGGTTG
3975	A65C	EF	gacgatgccttcagcacaAAAAGAACCCTGGTGAAG
3975	A65C	ER	CCCTGATAAAAGAGATGGA
3975	A65C	AR	gggacggtcggtagatCGCATGGGAGTCAGGGAT
3975	A65C	CR	gctggctcggtcaagaCGCATGGGAGTCAGGGAG
3976	A239G	EF	gacgatgccttcagcacaATGAGGGAGCAAGACAAG
3976	A239G	ER	TGATAAAAGAGATGGAAGGAG
3976	A239G	AR	gggacggtcggtagatGTCACTGTTTGTCACTGT
3976	A239G	GR	gctggctcggtcaagaGTCACTGTTTGTCACTGC
4206	A304T	EF	gacgatgccttcagcacaCTTTTAGCCAAGTGGAG
4206	A304T	ER	GGATCTGAGGAATCTGTG
4206	A304T	AR	gggacggtcggtagatACCAGGCAGAGAGAAAAAT
4206	A304T	TR	gctggctcggtcaagaACCAGGCAGAGAGAAAAA
4912	A74G	EF	CTTCACTGAGCGTCCGCAGAG
4912	A74G	ER	CCGTCGGCCCCGATTCA
4912	A74G	AR	CAGGCGAGCCTCAGCCCT
4912	A74G	GR	CAGGCGAGCCTCAGCCCC
4925	A251C	EF	TCATTTCCCAATTTACCTCC
4925	A251C	ER	CCTCTTTCCCATCTCCCT
4925	A251C	AF	gggacggtcggtagatAGCCAGGAGCCTGCGTCA
4925	A251C	CF	gctggctcggtcaagaAGCCAGGAGCCTGCGTCC

baySNP	SNP	Name	Sequence
4966	A251G	EF	CATTGCTCTTCCTCTCTGT
4966	A251G	ER	GTGTCATCATTCTTTCTTG
4966	A251G	AR	gggacggtcggtagatTCAGAGACATGAGTCCAT
4966	A251G	GR	gctggctcggtcaagaTCAGAGACATGAGTCCAC
5014	A2057G	ER	gacgatgccttcagcacaCACCTGTCCCACCCTATTT
5014	A2057G	EF	GTCCTGAACCCCCATTCT
5014	A2057G	AF	gggacggtcggtagatGCCTGCACTGCGTTCCTA
5014	A2057G	GF	gctggctcggtcaagaGCCTGCACTGCGTTCCTG
5296	A251G	EF	GCTCCTCTGCCTTCTGCTT
5296	A251G	ER	ATTTGCCCACTGCCCTTC
5296	A251G	AF	gggacggtcggtagatTGGCTGCAGGTGCGTCCA
5296	A251G	GF	gctggctcggtcaagaTGGCTGCAGGTGCGTCCG
5298	C172T	EF	GCCACACACACCTTAACA
5298	C172T	ER	AAAGTTCTCTGCCTCCAA
5298	C172T	CF	gggacggtcggtagatAGCTCTCAGCTGGGGTGC
5298	C172T	TF	gctggctcggtcaagaAGCTCTCAGCTGGGGTGT
5457	A134G	EF	AGCAGAATGGGCAATAGA
5457	A134G	ER	AGAGATGTGGGCAGAGAA
5457	A134G	AF	gggacggtcggtagatGGAAAGCCTACTTTCTTA
5457	A134G	GF	gctggctcggtcaagaGGAAAGCCTACTTTCTTG
5704	C61T	EF	ACAGCCATAACAGGAGTG
5704	C61T	ER	GGGTACTCAACCTAAGAGA
5704	C61T	CR	gggacggtcggtagatGTTCTCTTTGGGAAAACG
5704	C61T	TR	gctggctcggtcaagaGTTCTCTTTGGGAAAACA
5717	A1960G	EF	gacgatgccttcagcacaGAACAGAAACCACAGAACC
5717	A1960G	ER	GTCCCACCCTATTTTGAG
5717	A1960G	AR	gggacggtcggtagatCACTGGCCACCTCCCTT
5717	A1960G	GR	gctggctcggtcaagaCACTGGCCACCTCCCTC
5959	A71G	EF	gacgatgccttcagcacaACCATGCCTGACTTAACC
5959	A71G	ER	TTGTTTCCTGTCTCTTTC
5959	A71G	AR	gggacggtcggtagatGTTAAGAGGCTGGGCAGT
5959	A71G	GR	gctggctcggtcaagaGTTAAGAGGCTGGGCAGC
6162	C340G	EF	gacgatgccttcagcacaAGTGTTGTTAGGAGCAAAG
6162	C340G	ER	CTTAGGAAACTGAGGTGG

baySNP	SNP	Nam	Sequence
6162	C340G	CR	gggacggtcggtagatCTGCAGCCTGGGCAACAG
6162	C340G	GR	gctggctcggtcaagaCTGCAGCCTGGGCAACAC
6236	C906T	ER	gacgatgccttcagcacaTGGACACATTGAGCTTT
6236	C906T	EF	CTTCCCCAGAGATGACTAC
6236	C906T	CF	gggacggtcggtagatCCCCATCCTACTCAGCAC
6236	C906T	TF	gctggctcggtcaagaCCCCATCCTACTCAGCAT
6744	C348T	ER	gacgatgccttcagcacaGGTTACAGTGAGCCAAGA
6744	C348T	EF	AGGTGAAGAAAGCAAAATAC
6744	C348T	CF	gggacggtcggtagatTGGTGTGTGTTTTGTTTC
6744	C348T	TF	gctggctcggtcaagaTGGTGTGTGTTTTGTTTT
7133	C63G	EF	TTGAGACCCTACAGAGCCA
7133	C63G	ER	GGCAAGCTGAGGTGAAAG
7133	C63G	CR	gggacggtcggtagataATAAGGTAAGAAATGAG
7133	C63G	GR	gctggctcggtcaagaATAAGGTAAGAAATGAC
8210	A251G	EF	TAATTTCTAATGGCCTTCC
8210	A251G	ER	TCACTTACTCCCTGATGTCT
8210	A251G	AR	gggacggtcggtagatCATTGGGTTTTCCCTCAT
8210	A251G	GR	gctggctcggtcaagaCATTGGGTTTTCCCTCAC
8592	C46T	ER	gacgatgccttcagcacaACATTTAGTGCCAACATCAC
8592	C46T	EF	CTCTTCCCTGAGACACCA
8592	C46T	CF	gggacggtcggtagatGAAGGTGAAGGCCAGAGC
8592	C46T	TF	gctggctcggtcaagaGAAGGTGAAGGCCAGAGT
8943	A251C	EF	GAGGCTGAGACAGAAGAA
8943	A251C	ER	GTTTGACATTAAAGAAAATGAG
8943	A251C	AR	gggacggtcggtagatGGCTGGAGTGCAGTGATT
8943	A251C	CR	gctggctcggtcaagaGGCTGGAGTGCAGTGATG
9193	C88G	EF	CACGCTGTTGAGTGGG
9193	C88G	ER	CGCAGGTCTACGGTCA
9193	C88G	CR	gggacggtcggtagatCCCGGGTCTGAGGCTGCG
9193	C88G	GR	gctggctcggtcaagaCCCGGGTCTGAGGCTGCC
9516	A187G	EF	CACACACACACACACAC
9516	A187G	ER	GGTCCCTTACTTTCTCTT
9516	A187G	AR	gggacggtcggtagatCCTATCCCTACTTCCCCT
9516	A187G	GR	gctggctcggtcaagaCCTATCCCTACTTCCCCC

baySNP	SNP	Nam	Sequence
9698	A251G	EF	GTGACCCCAAAAGAGAGA
9698	A251G	ER	CTAGCTTGTTACTGCCTCC
9698	A251G	AF	gggacggtcggtagatGGCACGACCCCGCCCCCA
9698	A251G	GF	gctggctcggtcaagaGGCACGACCCCGCCCCCG
9883	A249G	EF	TCCACAACCTCAAAACCAC
9883	A249G	ER	CACAGTCCTGCAAGCTCA
9883	A249G	AR	gggacggtcggtagatCCGTGGCCGTGGCTCACT
9883	A249G	GR	gctggctcggtcaagaCCGTGGCCGTGGCTCACC
10481	A107T	ER	gacgatgccttcagcacaGTCGGGGCTCCACTT
10481	A107T	EF	TAGCGGGACAGCGCTG
10481	A107T	AF	gggacggtcggtagatCCCGGCGCGCCTCGGAGA
10481	A107T	TF	gctggctcggtcaagaCCCGGCGCGCCTCGGAGT
10542	C367T	EF	gacgatgccttcagcacaAATACACTGGGTCCTGCT
10542	C367T	ER	ATACTGCTGGCCTTTCTC
10542	C367T	CR	gggacggtcggtagatGGTCAGGGGAGCCCAGAG
10542	C367T	TR	gctggctcggtcaagaGGTCAGGGGAGCCCAGAA
10600	A251G	EF	CCTGGCAACTAACCTCTT
10600	A251G	ER	AGGCAGTCTCTGTCTACTC
10600	A251G	AR	gggacggtcggtagatATTGGCCCTGCTCAGGAT
10600	A251G	GR	gctggctcggtcaagaATTGGCCCTGCTCAGGAC
10621	C402T	EF	CCAGCCCTAAACCTAAA
10621	C402T	ER	AACCTCTCAAGATCAGACAC
10621	C402T	CF	gggacggtcggtagatTTAGCACTTAATAAGTAC
10621	C402T	TF	gctggctcggtcaagaTTAGCACTTAATAAGTAT
10745	A251G	EF	CCCCACAACAAAGAAAGA
10745	A251G	ER	GAAGCCAACCTCTCCAACA
10745	A251G	AF	gggacggtcggtagatCAAGGATTTCAAAAACCA
10745	A251G	GF	gctggctcggtcaagaCAAGGATTTCAAAAACCG
10771	C64G	EF	gacgatgccttcagcacaCCAGGGAAGAGCAGAACC
10771	C64G	ER	TGTACGGGAAGAGGCAGA
10771	C64G	CR	gggacggtcggtagatAGGGTGACACAGGCCACG
10771	C64G	GR	gctggctcggtcaagaAGGGTGACACAGGCCACC
10870	A251G	EF	ATCCCATCCCAACACACA
10870	A251G	ER	CCGAGACCAAACTCATTCAC

baySNP	SNP	Name	Sequence
10870	A251G	AR	gggacggtcggtagatGGCAGAGCCTGAGTCACT
10870	A251G	GR	gctggctcggtcaagaGGCAGAGCCTGAGTCAACC
10877	A251C	EF	CCTGTTTCTCAACCTTCTC
10877	A251C	ER	ATGGTCTATGGAACCTAATCT
10877	A251C	AF	gggacggtcggtagatGCACTGATTCTGCTTCCA
10877	A251C	CF	gctggctcggtcaagaGCACTGATTCTGCTTCCC
10948	G140T	EF	AAGGACAGGGTCAGGAAAG
10948	G140T	ER	CAGAGGGAGGAAGGAGGT
10948	G140T	GF	gggacggtcggtagatATGGAGGAGGGTGTCTGG
10948	G140T	TF	gctggctcggtcaagaATGGAGGAGGGTGTCTGT
11001	C286T	EF	gacgatgccttcagcacaTTCCCAAAGACCCACA
11001	C286T	ER	CCTCCACCGCTATCAC
11001	C286T	CR	gggacggtcggtagatTGGCTGCAGGACGTCCAG
11001	C286T	TR	gctggctcggtcaagaTGGCTGCAGGACGTCCAA
11001	C286T	EF	TTCCCAAAGACCCACA
11001	C286T	ER	CCTCCACCGCTATCAC
11001	C286T	CR	gggacggtcggtagatTGGCTGCAGGACGTCCAG
11001	C286T	TR	gctggctcggtcaagaTGGCTGCAGGACGTCCAA
11073	C215G	EF	CCCAACCACCCGTTCC
11073	C215G	ER	GCGCGGGAGCTAGAGA
11073	C215G	CF	gggacggtcggtagatGAAGCTGCGGGCCGGACC
11073	C215G	GF	gctggctcggtcaagaGAAGCTGCGGGCCGGACG
11153	C116T	EF	CGAGTGGGAAGAAAAGTAGA
11153	C116T	ER	ATGACTGCCTGCCTAGAA
11153	C116T	CR	gggacggtcggtagatAAGATAGGGTAGAGGCCG
11153	C116T	TR	gctggctcggtcaagaAAGATAGGGTAGAGGCCA
11210	C194T	EF	GAGGAGTGAGGGAAGTAAG
11210	C194T	ER	AAATGGAGAGAGATGGGA
11210	C194T	CF	gggacggtcggtagatCCAGGAAATGACATGATC
11210	C194T	TF	gctggctcggtcaagaCCAGGAAATGACATGATT
11248	C225T	EF	TGAGTTGAACAGCACTTGG
11248	C225T	ER	AGGGTAAGGGAGGGAAAA
11248	C225T	CR	gggacggtcggtagatTGATTCTTTCGCTTGCGG
11248	C225T	TR	gctggctcggtcaagaTGATTCTTTCGCTTGCA

baySNP	SNP	Name	Sequence
11372	A251G	EF	TAGAAAAGAAGAAAAATCAA
11372	A251G	ER	ACACACACACACACACAC
11372	A251G	AR	gggacggtcggtagatCATCACCTTTTAGTTTCT
11372	A251G	GR	gctggctcggtcaagaCATCACCTTTTAGTTTCC
11449	C251G	EF	ACAGAAGAACAACAACAAAAC
11449	C251G	ER	TGCGTATGAGGTAAAGAGA
11449	C251G	CF	gggacggtcggtagatATGAGTGAAGCCTGTCTC
11449	C251G	GF	gctggctcggtcaagaATGAGTGAAGCCTGTCTG
11450	A251T	EF	ACAGAAGAACAACAACAAAAC
11450	A251T	ER	TGCGTATGAGGTAAAGAGA
11450	A251T	AR	gggacggtcggtagatGGACCATAATCTTGAAGT
11450	A251T	TR	gctggctcggtcaagaGGACCATAATCTTGAAGA
11470	C251T	EF	GCTTGTCTTGTCTGATAGGTG
11470	C251T	ER	CAACGTGAGAATTTCCAAAAT
11470	C251T	CR	gggacggtcggtagatTGAGAATTTCCAAAATAG
11470	C251T	TR	gctggctcggtcaagaTGAGAATTTCCAAAATAA
11472	A251T	EF	TACATTCAAGGCAAGAAAA
11472	A251T	ER	TGATTAGTTACAATTACCTCTAGTATC
11472	A251T	AF	gggacggtcggtagatAGTTTGTCTAGTAAATGTA
11472	A251T	TF	gctggctcggtcaagaAGTTTGTCTAGTAAATGTT
11487	A485T	EF	gacgatgccttcagcacaAGAGAGCAGCTAGACTGAGA
11487	A485T	ER	TTCTTGCAAACAGTTGAG
11487	A485T	AR	gggacggtcggtagatAGTTGAGGGCTCAGGATT
11487	A485T	TR	gctggctcggtcaagaAGTTGAGGGCTCAGGATA
11488	C533G	EF	gacgatgccttcagcacaAGAGAGCAGCTAGACTGAGA
11488	C533G	ER	GTAAATAAAATGGGATGGTG
11488	C533G	CR	gggacggtcggtagatGCCCCAGCAAGCTGCATG
11488	C533G	GR	gctggctcggtcaagaGCCCCAGCAAGCTGCATC
11493	A171G	EF	CCTTTTGTGTTTTGTTTTGT
11493	A171G	ER	CTTCTCCACCTTCCATTC
11493	A171G	AF	gggacggtcggtagatGGGAACTCCTAAATCAA
11493	A171G	GF	gctggctcggtcaagaGGGAACTCCTAAATCAAG
11502	C455T	EF	gacgatgccttcagcacaACGATGGGGTCAGAGTCA
11502	C455T	ER	CCTACATTTACACACGAACA

baySNP	SNP	Name	Sequence
11502	C455T	CR	gggacggctcggtagatACACACTCCTCTCTCAAG
11502	C455T	TR	gctggctcggtcaagaACACACTCCTCTCTCAAA
11534	G258T	EF	GCCATCGTCTTTCCCT
11534	G258T	ER	TCCTCCCTCCTTCTCTCT
11534	G258T	GR	gggacggctcggtagatCCTCCACCCACCAGGGCC
11534	G258T	TR	gctggctcggtcaagaCCTCCACCCACCAGGGCA
11537	A251G	EF	CCTCTTTCTCCTCCTCTTC
11537	A251G	ER	CTCTTCCTGTCTTCTCCTCT
11537	A251G	AF	gggacggctcggtagatAGATGGACCTCTACAGGA
11537	A251G	GF	gctggctcggtcaagaAGATGGACCTCTACAGGG
11560	A185G	EF	CTCCTCCAACCTCCTTTAC
11560	A185G	ER	ATACTTCTCACTGCATCCT
11560	A185G	AR	gggacggctcggtagatCCTGTCCCCTCCCTAGTT
11560	A185G	GR	gctggctcggtcaagaCCTGTCCCCTCCCTAGTC
11594	C251T	EF	CACCTTCCTGAACTCACTC
11594	C251T	ER	TGATGTCTGTGCTGTCCT
11594	C251T	CR	gggacggctcggtagatTCTGGTCCACTCAAGGAG
11594	C251T	TR	gctggctcggtcaagaTCTGGTCCACTCAAGGAA
11624	C251T	EF	TCGGGAGGTGTAAGTAAG
11624	C251T	ER	CCACAGTCAGAAGAGACAA
11624	C251T	CR	gggacggctcggtagatAGAGACCCTGGTCCCAAG
11624	C251T	TR	gctggctcggtcaagaAGAGACCCTGGTCCCAAA
11627	C251T	EF	TTTATCACTACACCCCCTACTC
11627	C251T	ER	GACAGACCGACCAATCAC
11627	C251T	CR	gggacggctcggtagatCCCTGGGAAGGTTGAGAG
11627	C251T	TR	gctggctcggtcaagaCCCTGGGAAGGTTGAGAA
11650	A146G	EF	CTGTCTGTTTGGGTCTTC
11650	A146G	ER	CGTTGTTCTCTGTCCACT
11650	A146G	AR	gggacggctcggtagatGGCCAAATGTCTAAAAGT
11650	A146G	GR	gctggctcggtcaagaGGCCAAATGTCTAAAAGC
11654	A251G	EF	CGTATCTCTTGCCTTTCTT
11654	A251G	ER	CTTCTCTTATGCCTTCCC
11654	A251G	AF	gggacggctcggtagatTTACTTGAAAGGACACCA
11654	A251G	GF	gctggctcggtcaagaTTACTTGAAAGGACACCG

baySNP	SNP	Name	Sequence
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11655	A251C	ER	CTTCTCTTATGCCTTCCC
11655	A251C	AF	gggacggtcggtagatTTCTGCACTAAAGCTGTA
11655	A251C	CF	gctggctcggtcaagaTTCTGCACTAAAGCTGTC
11656	C251T	EF	TGGGAAGAAAAGAGAAG
11656	C251T	ER	GTTGAAACACTGCACAAG
11656	C251T	CR	gggacggtcggtagatCAGGGCTGTTGGGTGAAG
11656	C251T	TR	gctggctcggtcaagaCAGGGCTGTTGGGTGAAA
11825	A277G	ER	gacgatgccttcagcacaTGAATAGACAGGGACGAA
11825	A277G	EF	GACCTTGGAATAATGGAG
11825	A277G	AF	gggacggtcggtagatCAACCCAGCAAAAATGGA
11825	A277G	GF	gctggctcggtcaagaCAACCCAGCAAAAATGGG
11914	A246T	EF	gacgatgccttcagcacaTTGGAAGTGAGATAAGATAGGT
11914	A246T	ER	ACGGTGAGAATGAGAGGT
11914	A246T	AR	gggacggtcggtagatAAAACAGACATCAGAGGT
11914	A246T	TR	gctggctcggtcaagaAAAACAGACATCAGAGGA
12097	A411G	ER	gacgatgccttcagcacaGATGAAACCCTGTCTCTACT
12097	A411G	EF	TTATCAACCTTAGTCTCCCT
12097	A411G	AF	gggacggtcggtagatACCTGCCACCACACCCAA
12097	A411G	GF	gctggctcggtcaagaACCTGCCACCACACCCAG
12366	A412G	ER	gacgatgccttcagcacaGCTGATGTGGTTGTGAG
12366	A412G	EF	GTTCTGTAGCTCGTGTAG
12366	A412G	AF	gggacggtcggtagatCTCCCCGCCCTGCAGCAA
12366	A412G	GF	gctggctcggtcaagaCTCCCCGCCCTGCAGCAG
12619	A25G	ER	gacgatgccttcagcacaTGGCTGGACTTTGACTGATA
12619	A25G	EF	TCTTGTTTGTGTCACAGTGC
12619	A25G	AF	gggacggtcggtagatTGTGTCACAGTGCTCTGA
12619	A25G	GF	gctggctcggtcaagaTGTGTCACAGTGCTCTGG
13025	A585C	EF	gacgatgccttcagcacaTTTAAGTAACATGACAAACTC
13025	A585C	ER	ATCTGATAACTGAGCAGG
13025	A585C	AR	gggacggtcggtagatCTATTAAGTAACTGGTGT
13025	A585C	CR	gctggctcggtcaagaCTATTAAGTAACTGGTGG
13191	A504G	ER	gacgatgccttcagcacaATTCTCCCATTCTCCTGT
13191	A504G	EF	TGCCTCTTCTCCTCATTC

baySNP	SNP	Name	S quence
13191	A504G	AF	gggacggtcggtagatCCCTAATGTCTTCCTCTGA
13191	A504G	GF	gctggctcggtcaagaCCCTAATGTCTTCCTCTGG
900045	C116T	EF	ATCTCCTGATCCAAGTCC
900045	C116T	ER	CACACTGTGCCCATCTAC
900045	C116T	CR	gggacggtcggtagatCTGACTGATTACCTCATG
900045	C116T	TR	gctggctcggtcaagaCTGACTGATTACCTCATA
900078	A251G	EF	CATAGGTAAAGATCTGTAGGTG
900078	A251G	ER	CCACCTTGGAAGTTGGCAA
900078	A251G	AR	gggacggtcggtagatattaaatcgectctctcT
900078	A251G	GR	gctggctcggtcaagaattaaatcgectctctcC
900107	C426T	ER	gacgatgccttcagcacaAGGGCTTTTTCAGGTAGA
900107	C426T	EF	GACCTTTCCTGGGTAGAA
900107	C426T	CF	gggacggtcggtagatACTCTGAACCTGGGGGAC
900107	C426T	TF	gctggctcggtcaagaACTCTGAACCTGGGGGAT
10000002	A103G	AF	gggacggtcggtagatGATCAACACAATCTTCAA
10000002	A103G	EF	CAGCTGAAAGAGATGAAATTTACT
10000002	A103G	ER	GACGATGCCTTCAGCACAACTTATGAAGATTAAGGCATAGG
10000002	A103G	GF	gctggctcggtcaagaGATCAACACAATCTTCAG
10000006	G107A	AF	gctggctcggtcaagaGGGCTGGGCTGCTAGGGA
10000006	G107A	EF	AGACGAGTTCAAGGTGAGTG
10000006	G107A	ER	GACGATGCCTTCAGCACACCAAGTTTCCGAGTTTCC
10000006	G107A	GF	gggacggtcggtagatGGGCTGGGCTGCTAGGGG
10000014	A153C	AF	gggacggtcggtagatGTACCAATACATCCTGCA
10000014	A153C	CF	gctggctcggtcaagaGTACCAATACATCCTGCC
10000014	A153C	EF	CTGCTGATGTCTCTGTTG
10000014	A153C	ER	GACGATGCCTTCAGCACAGACTTACTTTGCTCACACTT
10000025	C291T	CF	gggacggtcggtagatCCTCACTTCCTCAACGCC
10000025	C291T	EF	CCTCTCTGTCTGTTATCTTG
10000025	C291T	ER	GACGATGCCTTCAGCACAGTGTGCCTCCTGGTTAG
10000025	C291T	TF	gctggctcggtcaagaCCTCACTTCCTCAACGCT

Table 2b **Oligonucleotide primers used for genotyping using Pyro-sequencing**

5 The baySNP number refers to an internal numbering of the PA SNPs. Primer sequences are listed for preamplification of the genomic fragments and for sequencing of the SNP using the pyrosequencing method. Bio: Biotinylated Oligonucleotide.

BaySNP	Name	Sequence
2995	Primer F	GCCAAGACTAGGAAGTAAGTGT
2995	Primer R	Bio- CCCAGAACCACAAAGCTAGTAA
2995	Seq.	TGCCCTGGTCACCTCCTTTCC
3689	Primer F	BIO-CTGACCCTGACCTTCATACTCAA
3689	Primer R	AGAAGAAAGAAGCCTCTCTACAGTT
3689	Seq.	AACAGATCAGGTTGGTG
4838	Primer F	Bio-CAAAGATGACCTTATGGCTCTGA
4838	Primer R	GTCTCGGAACATGACCTTTAGT
4838	Seq.	TGACTAAGAATGTAATGGGGAAGA
6498	Primer F	CTTTGTGGATCTTTCTGCGGTGT
6498	Primer R	Bio-CCATGTTGAGGAGCCCAGAGTGA
6498	Seq.	ATTACAGTTGTGAGATTGTGC
8021	Primer F	GGCCTTCTATGTACTAGGCG
8021	Primer R	Bio-CTCTTTCTGGAGGCATCAATC
8021	Seq.	CACAGGGAGACCCC
8060	Primer F	Bio-GCCTTATTTTCCACTCCCACCT
8060	Primer R	TACCTTTCCCCATCCCAACTG
8060	Seq.	TCAGCATATGTTTGGATT
8846	Primer F	ATTTGAGAGAAGGTAGGGT
8846	Primer R	BIO-TTGTTACTCTGTAGCCA
8846	Seq.	AAATATTCAGTAACTTGTTT
9849	Primer F	AAG CAG CAA TCG AAT CCC TT
9849	Primer R	TGT TGT TGT TTG GCT AGC TCC

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BaySNP	Name	Sequence
9849	Seq.	CCT GCC TTA CTG AGA GCC AAA
10079	Primer F	Bio-CACGCCAATTCCCACCATCCT
10079	Primer R	GTCCGTCGAGGGGGAATGTGTTT
10079	Seq.	AATGTGTTTCTTGGGGGT
10747	Primer F	CTAACCATCTTCCAAATGCTTAATC
10747	Primer R	BIO-TCCTTGAGTCTGAGTTTCCC
10747	Seq.	CACAAGAAACCCTGAAA
11578	Primer F	CTC GGC GTG CTT GGT AAT AA
11578	Primer R	CGG AGC CGA ACT CTG GAG GAA TCT
11578	Seq.	GGC TGG CAA GTT GTT CCA TCC CAC
11644	Primer F	TGA GCA GCG CAT CCT
11644	Primer R	TGC AGC CCA CTG ACT CAA
11644	Seq.	GCT GTT ACT CAG TAT GAT
12008	Primer F	CCGAAGACCAAGACGC
12008	Primer R	Bio-TCTTCCATAAAAACAAGGCTC
12008	Seq.	AAACAAGAAATTCTGTTTA
13937	Primer F	TGA CAG CTC CCA TTG GAA
13937	Primer R	AAT TAA TGC GAT CCC TC
13937	Seq.	GAC AGC TCC CAT TGG AAG
900002	Primer F	ATTGGGCAGGGATAAGAGAAAAG
900002	Primer R	Bio-GATGAATCACAGAATGCGGTAT
900002	Seq.	CACACAGCAGTTCACGCA
900013	Primer F	GCCAAGACTAGGAAGTAAGTGT
900013	Primer R	Bio- CCCAGAACCACAAAGCTAGTAA
900013	Seq.	TGCCCTGGTCACCTCCTTTGC
900025	Primer F	Bio-AGTGGCTCACTTGCTAACG
900025	Primer R	CTGGGGAAGAAAATAAATGAA
900025	Seq.	CTTGCTCTTAGGATACACGT
900032	Primer F	AGCGTCTTCACCATCTGCT
900032	Primer R	Bio-GGGAAGGAGGAAGCCAAACA
900032	Seq.	ACATGTCTGATGATACCTGG

BaySNP	Nam	Sequence
900045	Primer F	BIO-GCCATGCACGATTTCCC
900045	Primer R	CACTGTGCCCATCTACGAG
900045	Seq.	GGACCTGACTGATTACCT
900065	Primer F	GAGTAGCTAGGATCACAGGTGCGT
900065	Primer R	BIO-TGTTCGAGATTTAAGAAAGTTGGC
900065	Seq.	CAGGTGCGTGCCACCATGCCC
900082	Primer F	CAC ACA ATT TTC CAC TTA
900082	Primer R	GAC TCC AGT TTT CTA TCA
900082	Seq.	ATG TTG ATG TAA TCT ACT
900096	Primer F	TGGGGCAAGCAACAGTGGT
900096	Primer R	Bio-TAGGCAGGGCAAGGGATTAGG
900096	Seq.	TTTAAATTCTCTGACAGAGAC
900107	Primer F	BIO-GCCACCAGCCCACACTCTGAACCTG
900107	Primer R	CCATCAGCCTTCACCCACGTGCCA
900107	Seq.	GCCTCAGCTTGACCT
900115	Primer F	Bio-GGTAAGTGCGTGCCTGGGAGATGC
900115	Primer R	CGGGGTGGGGAGGACAGAGC
900115	Seq.	GAGGACAGAGCAAAAGGAT
900121	Primer F	Bio-TGCCTTACAATATACAATGG
900121	Primer R	CAATGGGTAAGGAGTAAAGTT
900121	Seq.	TTCCAGCTGCTTTTA

Table 2c**Oligonucleotide primers used for genotyping using Restriction Fragment
Length Polymorphism (RFLP)**

The baySNP number refers to an internal numbering of the PA SNPs. Primer sequences are listed for preamplification of the genomic fragments. The restriction enzyme used for RFPL is indicated.

baySNP	Name	Sequence	Enzyme
900173	Primer F	GAACAAACCTCCGAGATGCTAC	Hind III
900173	Primer R	GTCTTATGTTACTGGGCTTTCACC	Hind III

Table 2d Oligonucleotide primers used for genotyping using TaqMan

The baySNP number refers to an internal numbering of the PA SNPs. Primer sequences are listed for amplification of the genomic fragments. In addition the respective fluorescent hybridisation probes are listed. If not otherwise stated, all fluorescent probes have a 'minor groove binder' (MGB) attached (Kutyavin et al., Nucleic Acids Research 2000, 28:655-661).

baySNP	F-Sequence	R-Sequence	VIC-MGB	FAM-MGB
52	CACCCCTAGAAATTCACATTAATTTCAAC	GGCCTTGAAGAAGATTATTATTTGAGAA	CTATGCATACCTTTTGC	ATGCATAGTTTTCATTAT
542	TTTCGCTCCATCAACCAAGTC	GATGGGTGATCAGCCGAATC	CAATTGGaGTTGGAGG	AATTGGgGTTGGAGG
821	GCCCAAGTTATACCTCAGTGTGTAAC	AGGTCAGTACAGAGGATCATGAGA	TGTGATACCTTGGaACAG	CTGTGATACCTGGcACA
1056	TGTATGCAGTCGCGTGATCTG	CGCCCTCGGCACCTCTTG	CCAAACaACAGGACGG	AAACagCAGGACGGG
1204	CTGTAAGCATCTGGAATGTCTATGA	GGCTCAGTCTTTGATCTTTAGCAAG	CACTCACATTAAATTAG	ACTCACATTACAATTAGT
1722	GGACCCCTAAGAACCCCAAGAT	ATGGGCTTAACACAGGAGATGATG	TGGCCTGGCGgTG	TGGCCTGGCGaTGT
1757	ACAGGGCTGCAGCCAC	AGCCTCTGCCCTCCTCCA	AACCAAAATGaAGGAGAG	ACCAAAATGgAGGAGAG
1765	GGAGCTGTGAGGTATGGGCTT	TGTCAAGATGCAGCTGAAGGTC	ACGGAGGAAGAGGT	ACGGAGGAAGAaGT
1799	TTTGGTGGGTGTCAATTGACA	TGGACATATGGGCGGACTCT	AGTGTGATCaTCACTTT	CAGTGTGATCgTCACT
1837	CACTCAGCCCTGCTCTTTCC	CATCCTTTGGCGGTCTTGGT	TGCAGGGcTACATGA	TCATGCAGGgTACAT
1870	CTGGCTCCTGACCCCTTGCT	GGAGGATGCCATCTCGAACA	TGCCTCCTTcTCAcAC	CCTCCTTlTcCACACGGA
1988	CCGTGGCTTCATGGTGACT	CTACCTGTCCGGTGCATCATC	TCCTATACcGTGGGTGT	CTATACcGTGGGTGTcAT
2000	TTCTCACTGTGATATATAAACTCAGACCC	CGATGAACAGTTGGAAATAGGTTGT	TACTCATcTTCCTAAATTAC	CAAAATATCTACTCATlTTC
2085	TCATTACATCAGGTATATTGCACTGTAAA	TCAGAGACACTGAAGAACTTAAAGAAATC	TGTTACCGAaAaGANA	TGTTACCGAaAAATAAA
2281	GCTGCAATTGGAGAGGACTGATC	CGGTTAACTTATAAAGAAACCGATGTTT	CATACCACAAaCCA	ACCACAAaCCAGGTC
2298	TGCTAGTGTTCCTGGTTGCATATT	GGCACCGGTGTAGACTTGATCTAAA	TCATGGCaTTTCA	TATCATGGGcCTTTCA
2357	GCGAAGTTCGGACACCAA	GGTTACGTCGTCTTCGATCCT	AAGACGAaAATGaATC	AAGACGAaAATGgATC
4838	AAGATGACCTTATGGCTCTGAGATG	TCTCGGAACATGACCTTTAGTCTGT	AAGAAcTGCCCTGcCT	AAGAAcTGCCCTGcC
5320	GGGATATATAGTAGAaAAACAAAGCCTGTCT	CAACTTAATCACTACTACTCCATGTAAGCA	AAGGAAGCTGGaTATG	AGGAAGCTGGgTATGT

baySNP	F-Sequence	R-Sequence	VIC-MGB	FAM-MGB
5717	GGCCGCTCCTGGCT	AACCCACACCTTCAGTCTAGAAA	Vic- CCACCTCCCTCTAGCCTCAGTTGC -TAMRA	Fam- CCACCTCCCTCTAGCCTCAGTT- TAMRA
5959	ACCAGAAACAATGCCAACCA	CAGTGTGAACCAAGGATGTC	Vic- CGAATGTGCTGCCAGCC- TAMRA	Fam- TCGAATGTGaCTGCCAGCCTC- TAMRA
6482	CATAGTTTAGGATAAACAAAGGGATTCA	TGTCATGGAAACGCCACAAC	AACAGATCTGGTCTaCCT	AGATCTGGTCTgCCTC
8060	GCTATGGAATGGATGTGCTTATT	TGCATGGCATCAGCATATGTT	CCCACCTGGaGAAT	TCCCACCTGGgGAA
8816	CAGCCCTCTGCTCCAAG	TCCCTCTCTGTCCAGGC	TGAGAAAAAGgTTCCG	CTGAGAAAAAGcTTC
10600	GGTAGGTTTGGGCATCTC	AAGTTAATCAAGCCTTTTCAATTGG	TGCTCAGGATAGCC	TGCTCAGGACAGCC
10771	CTGGGCCACCGAGTTAC	GATCTCTGTGAGTGTGGTCTGT	AGGAAGcGTGGCCT	CAAGGAAGgGTGGC
10948	ACATTCCCCTTCCACGCTT	GCAGGGCAGAGGGAGGA	CGCCCAGTAATaCAGA	CCCAGTAATcCAGACAC
11001	GCCATCCTTGTGAACGTGAA	ACATGACCAGGGCCCACTT	TGTTCCaCTGGACGT	TTCCaTGGAGCTCCT
11073	GAGCAACAGCCGCTGAG	GCGGAGCTAGAGAGCAGTG	TGGCGCTgGTC	TCTGGCGCTcGT
11248	GAAAGCTAATCCCCCTGACG	TGAAGGGTAAGGGAGGGAAA	CTTGGCgTCGCGTC	TTGGCaTCGCGTCAG
11654	AGTTTGTCTTCTATTAGAGGTTTCCA	CTCTTATGCTTCCCCACCA	TTGAAAGGACACCaTATT	ACACCgTATTTTTTCAC
11655	CATATCAAGAAAGATTATCTCCAACCTT	TGAAACCTCTTAATAGGAAACAAACT	CACTAAGCTGTaATATTA	CTAAAGCTGTcATATTAC
13191	GAGTTGGTGGCATAAAACCCCTAA	CCGTGCCCCACCTTCTCTCTCT	TCTTCTCTGTgGTAACA	TCTTCTGaGTAAACAAC

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Table 3**PA SNPs, SNP classes and putative PA genes**

The baySNP number refers to an internal numbering of the PA SNPs. Listed are the different polymorphisms found in our association study. Also from the association study we defined SNP classes; with ADR being adverse drug reaction related, with EFF being drug efficacy related and CVD being cardiovascular disease related. ADR3 and ADR5 relate to advanced and severe ADR, whereas VEFF and UEFF relate to very high/low and ultra high/low drug efficacy (see table 1b). Also accession numbers and descriptions of those gene loci are given that are most homologous to the PA genes as listed in the sequences section (see below). Homologous genes and their accession numbers could be found by those skilled in the art in the Genbank database. Null: not defined.

baySNP	SNP class	GTTYPE1	1	GTTYPE1	2	GTTYPE2	NCBI	DESCRIPTION
28	EFF	CC		CT		TT	U15552	Human acidic 82 kDa protein mRNA, complete cds.
29	CVD	AA		AG		GG	HS162961	Human T-lymphoma invasion and metastasis inducing TIAM1 protein (TIAM1) mRNA, complete cds.
29	ADR3	AA		AG		GG	HS162961	Human T-lymphoma invasion and metastasis inducing TIAM1 protein (TIAM1) mRNA, complete cds.
29	ADR5	AA		AG		GG	HS162961	Human T-lymphoma invasion and metastasis inducing TIAM1 protein (TIAM1) mRNA, complete cds.
52	EFF	CC		CG		GG	X69907	H.sapiens gene for mitochondrial ATP synthase c subunit (P1 form)

BAVSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE1 2	GTTYPE2 2	NCBI	DESCRIPTION
56	EFF	AA	AG	AG	GG	M92357	Homo sapiens B94 protein mRNA, complete cds.
89	CVD	AA	AG	AG	null	L23982	Homo sapiens (clones: CW52-2, CW27-6, CW15-2, CW26-5, 11-67) collagen type VII intergenic region and (COL7A1) gene, complete cds.
90	CVD	CC	CT	CT	TT	M65212	Homo sapiens catechol-O-methyltransferase (COMT) mRNA, complete cds.
99	CVD	CC	CT	CT	TT	X96698	H.sapiens mRNA for D1075-like gene
140	EFF	CC	CT	CT	TT	M14335	Human coagulation factor V mRNA, complete cds.
152	EFF	AA	AG	AG	GG	M32670	Homo sapiens ITGB3 gene, intron 2, fragment C, partial sequence.
214	CVD	AA	AG	AG	GG	X66957	H. sapiens hexokinase I (MK-16)
221	CVD	CC	CG	CG	GG	X76732	H.sapiens mRNA for NEFA protein
224	CVD	CC	CT	CT	TT	M14764	Human nerve growth factor receptor mRNA, complete cds.
294	CVD	CC	CT	CT	TT	P02568	ACTIN, ALPHA SKELETAL MUSCLE (ALPHA-ACTIN 1).
307	CVD	CC	CT	CT	TT	X63546	H.sapiens mRNA for tre oncogene (clone 210)
411	CVD	AA	AT	AT	TT	HS34804	Human thermostable phenol sulfotransferase (STP2) gene, partial cds.
449	CVD	CC	CG	CG	GG	M36341	Human ADP-ribosylation factor 4 (ARF4) mRNA, complete cds.

BAYSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE1 2	GTTYPE2	NCBI	DESCRIPTION
466	CVD	CC	CT	TT	TT	AF129756	Homo sapiens MSH55 gene, partial cds; and CLIC1, DDAH, G6b, G6c, G5b, G6d, G6e, G6f, BAT5, G5b, CSK2B, BAT4, G4, Apo M, BAT3, BAT2, AIF-1, 1C7, LST-1, LTB, TNF, and LTA genes, complete cds.
472	EFF	AA	AG	GG	GG	M57965	Homo sapiens (clones lambda gMHC 1,2,3 and 4) beta-myosin heavy chain (MYH7) gene, complete cds.
542	CVD	AA	AG	GG	GG	M64082	Human flavin-containing monooxygenase (FMO1) mRNA, complete cds.
542	ADR	AA	AG	GG	GG	M64082	Human flavin-containing monooxygenase (FMO1) mRNA, complete cds.
739	CVD	CC	CG	GG	GG	L43509	Homo sapiens methionine adenosyltransferase alpha subunit gene fragment.
821	CVD	AA	AC	CC	CC	X80507	H.sapiens YAP65 mRNA
821	VEFF	AA	AC	CC	CC	X80507	H.sapiens YAP65 mRNA
1005	CVD	AA	AG	GG	GG	M81357	Human coagulation factor VII (F7) gene exon 1 and factor X (F10) gene, exon 1.
1055	CVD	AA	AT	TT	TT	J02758	Human apolipoprotein A-IV gene, complete cds.
1056	EFF	AA	AG	GG	GG	Q16720	CALCIUM-TRANSPORTING ATPASE PLASMA MEMBRANE, ISOFORMS 3A/3B (EC 3.6.1.38) (CALCIUM PUMP) (PMCA3).

BAYSNP	SNP class	GT/YPE1 1	GT/YPE1 2	GT/YPE2 2	NCBI	DESCRIPTION
1085	CVD	AA	AG	GG	M14564	Human cytochrome P450c17 (steroid 17-alpha-hydroxylase/17,20 lyase) mRNA, complete cds.
1086	CVD	AA	AG	GG	M14564	Human cytochrome P450c17 (steroid 17-alpha-hydroxylase/17,20 lyase) mRNA, complete cds.
1092	CVD	CC	CG	GG	AF022375	Homo sapiens vascular endothelial growth factor mRNA, complete cds.
1096	CVD	GG	GT	TT	X15323	H.sapiens angiotensinogen gene 5' region and exon 1
1101	EFF	CC	CT	TT	AL031005	Homo sapiens DNA sequence from PAC 329E20 on chromosome 1p34.4-36.13. Contains endothelin-converting-enzyme 1 (ECE-1), EST, STS, CA repeat
1204	CVD	AA	AG	GG	AC004264	Homo sapiens PAC clone RP1-102K2. from 22q12.1-qter, complete sequence.
1504	CVD	CC	CT	TT	AC005175	Homo sapiens chromosome 19, cosmid R31449, complete sequence.
1511	EFF	GG	GT	TT	AF009674	Homo sapiens axin (AXIN) mRNA, partial cds.
1524	ADR3	AA	AC	CC	AF223404	Homo sapiens WNT1 inducible signaling pathway protein 1 (WISPI) gene, promoter and partial cds.
1556	EFF	CC	CG	GG	L34058	Homo sapiens cadherin-13 mRNA, complete cds.
1561	CVD	AA	AC	CC	M31664	Human cytochrome P450 (CYP1A2) gene, exons 1 and 2.

BAYSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE1 2	NCBI	DESCRIPTION
1582	CVD	CC	CT	TT	AF050163	Homo sapiens lipoprotein lipase precursor, gene, partial cds.
1638	CVD	AA	AG	GG	AF090318	Homo sapiens sterol 12-alpha hydroxylase CYP8B1 (Cyp8b1) mRNA, partial cds.
1653	CVD	GG	GT	TT	J02846	Human tissue factor gene, complete cds.
1662	CVD	CC	CT	TT	K02402	Human coagulation factor IX gene, complete cds.
1714	CVD	AA	AG	GG	D50857	Human DOCK180 protein mRNA, complete cds.
1722	ADR5	CC	CT	TT	D73409	Homo sapiens mRNA for diacylglycerol kinase delta, complete cds.
1757	EFF	AA	AG	GG	J04046	Human calmodulin mRNA, complete cds.
1765	ADR3	AA	AG	GG	J05096	Human Na,K-ATPase subunit alpha 2 (ATP1A2) gene, complete cds.
1765	ADR5	AA	AG	GG	J05096	Human Na,K-ATPase subunit alpha 2 (ATP1A2) gene, complete cds.
1776	CVD	AA	AG	GG	L22569	Homo sapiens cathepsin B mRNA, 3' UTR with a stem-loop structure providing mRNA stability.
1799	CVD	CC	CT	TT	D21255	Human mRNA for OB-cadherin-2, complete cds.
1806	EFF	AA	AG	GG	AF106202	Homo sapiens endothelial cell protein C receptor precursor (EPCR) gene, complete cds.
1837	CVD	CC	CT	TT	J00098	Human apolipoprotein A-I and C-III genes, complete cds.
1837	ADR5	CC	CT	TT	X00566	Human mRNA for lipoprotein apoA1 Human apolipoprotein A-I and C-III genes, complete cds.

BAYSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE2 2	NCBI	DESCRIPTION
1837	ADR	CC	CT	TT	J00098	Human apolipoprotein A-I and C-III genes, complete cds.
1870	CVD	CC	CT	TT	M84820	Human retinoid X receptor beta (RXR-beta) mRNA, complete cds.
1882	CVD	CC	CT	TT	U06643	Human keratinocyte lectin 14 (HKL-14) mRNA, complete cds.
1988	CVD	CC	CT	TT	X61598	H.sapiens mRNA for collagen (a collagen-binding protein)
2000	CVD	CC	TT	null	P03915	NADH-UBIQUINONE OXIDOREDUCTASE CHAIN 5 (EC 1.6.5.3).
2000	ADR	CC	TT	null	P03915	NADH-UBIQUINONE OXIDOREDUCTASE CHAIN 5 (EC 1.6.5.3).
2071	CVD	AA	AG	GG	L04143	Human c-kit gene.
2078	CVD	GG	GT	TT	X77584	H.sapiens mRNA for ATL-derived factor/thirdoxin.
2085	VEFF	GG	GT	TT	X82540	H.sapiens mRNA for activin beta-C chain
2095	CVD	AG	GG	null	L34155	Homo sapiens laminin-related protein (LamA3) mRNA, complete cds.
2119	CVD	AA	AG	null	Z22535	H.sapiens ALK-3 mRNA.
2119	EFF	AA	AG	null	Z22535	H.sapiens ALK-3 mRNA.
2141	EFF	AA	AG	GG	AB035073	Homo sapiens mRNA for platelet glycoprotein VI, complete cds.
2141	CVD	AA	AG	GG	AB035073	Homo sapiens mRNA for platelet glycoprotein VI, complete cds.
2182	EFF	AA	AG	GG	D32046	Human gene for thrombopoietin, exon1-exon6, complete cds.

BAYSNP	SNP class	GTYP1 1	GTYP1 2	GTYP1 2	NCBI	DESCRIPTION
2234	CVD	GG	GT	TT	AC004264	Homo sapiens PAC clone RP1-102K2 from 22q12.1-qter, complete sequence.
2281	VEFF	AA	AC	CC	X87872	H.sapiens mRNA for hepatocyte nuclear factor 4c
2298	CVD	AA	AC	CC	V01511	H.sapiens gene for beta-nerve growth factor (beta-NGF)
2341	CVD	CC	CT	TT	J03280	Human phenylethanolamine N-methyltransferase gene, complete cds.
2357	CVD	AA	AG	GG	O15055	PERIOD CIRCADIAN PROTEIN 2 (KIAA0347).
2366	CVD	GG	GT	TT	P35414	PROBABLE G PROTEIN-COUPLED RECEPTOR APJ.
2423	CVD	AA	AG	GG	AF000571	Homo sapiens kidney and cardiac voltage dependent K+ channel (KvLQT1) mRNA, complete cds.
2708	CVD	CC	CT	TT	AL031005	Homo sapiens DNA sequence from PAC 329E20 on chromosome 1p34.4-36.13. Contains endothelin-converting-enzyme 1 (ECE-1), EST, STS, CA repeat
2995	ADR5	AA	AC	CC	ABCC1	ABCC1: ATP-binding cassette, sub-family C (CFTR/MRP), member 1
2995	UEFF	AA	AC	CC	ABCC1	ABCC1: ATP-binding cassette, sub-family C (CFTR/MRP), member 1
3360	ADR5	GG	GT	TT	ABCB4	ABCB4: ATP-binding cassette, sub-family B (MDR/TAP), member 4
3464	CVD	AA	AG	GG	M34668	Human protein tyrosine phosphatase (PTPase-alpha) mRNA.

BAYSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE2 2	NCBI	DESCRIPTION
3689	EFF	CC	CG	GG	M95724	H.sapiens centromere autoantigen C (CENPC) mRNA, complete cds.
3975	UEFF	AA	AC	CC	U43368	Human VEGF related factor isoform VRF186 precursor (VRF) mRNA, complete cds.
3976	UEFF	AA	AG	GG	U43368	Human VEGF related factor isoform VRF186 precursor (VRF) mRNA, complete cds.
4206	ADR3	AA	AT	TT	BC000006	Homo sapiens, ATPase, Na+/K+ transporting, beta 1 polypeptide
4838	VEFF	AA	AG	GG	L08246	Human myeloid cell differentiation protein (MCL1) mRNA.
4912	EFF	AA	AG	GG	AF022375	Homo sapiens vascular endothelial growth factor mRNA, complete cds.
4925	CVD	AA	AC	CC	AF036365	Homo sapiens caveolin-3 (CAV3) mRNA, complete cds.
4966	ADR3	AA	AG	GG	AF133298	Homo sapiens cytochrome P450 (CYP4F8) mRNA, complete cds.
5014	ADR5	AA	AG	GG	AL008637	Human DNA sequence from clone CTA-833B7 on chromosome 22q12.3-13.2 Contains the NCF4 gene for cytosolic neutrophil factor 4 (40kD), the 5' part of the CSF2RB gene for granulocyte-macrophage low-affinity colony stimulating factor 2 receptor beta, ESTs, STS
5296	CVD	AA	AG	GG	J02933	Human blood coagulation factor VII gene, complete cds.
5296	EFF	AA	AG	GG	J02933	Human blood coagulation factor VII gene, complete cds.

BAVSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE1 2	GTTYPE2 2	NCBI	DESCRIPTION
5298	EFF	CC	CT	CT	TT	J02933	Human blood coagulation factor VII gene, complete cds.
5298	CVD	CC	CT	CT	TT	J02933	Human blood coagulation factor VII gene, complete cds.
5320	EFF	AA	AG	AG	GG	J03799	Human colin carcinoma laminin-binding protein mRNA, complete cds.
5361	CVD	AA	AC	AC	CC	L02932	Human peroxisome proliferator activated receptor mRNA, complete cds.
5457	EFF	AA	AG	AG	GG	L29529	Homo sapiens (clone HHT-1 variant harboring HH-05) cardiac L-type voltage dependent calcium channel alpha 1 subunit (CACNL1A1) mRNA, complete cds.
5704	CVD	CC	CT	CT	TT	M58050	Human membrane cofactor protein (MCP) mRNA, complete cds.
5717	ADR3	AA	AG	AG	GG	AL008637	Human DNA sequence from clone CTA-833B7 on chromosome 22q12.3-13.2 Contains the NCF4 gene for cytosolic neutrophil factor 4 (40kD), the 5' part of the CSF2RB gene for granulocyte-macrophage low-affinity colony stimulating factor 2 receptor beta, ESTs, STS
5959	CVD	AA	AG	AG	GG	HSHMGOAS	H.sapiens mRNA for 3-hydroxy-3-methylglutaryl coenzyme A synthase
5959	ADR5	AA	AG	AG	GG	HSHMGOAS	H.sapiens mRNA for 3-hydroxy-3-methylglutaryl coenzyme A synthase

BAYSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE1 2	NCBI	DESCRIPTION
5959	ADR	AA	AG	GG	HSHMGOAS	H.sapiens mRNA for 3-hydroxy-3-methylglutaryl coenzyme A synthase
6162	ADR3	CC	CG	GG	AF005896	Homo sapiens Na K-ATPase beta-3 subunit (atp1b3) gene, exon 7 and complete cds.
6162	ADR	CC	CG	GG	AF005896	Homo sapiens Na K-ATPase beta-3 subunit (atp1b3) gene, exon 7 and complete cds.
6162	ADR5	CC	CG	GG	AF005896	Homo sapiens Na K-ATPase beta-3 subunit (atp1b3) gene, exon 7 and complete cds.
6236	ADR5	CC	CT	TT	HSU62961	Human succinyl CoA:3-oxoacid CoA transferase precursor (OXCT) mRNA, complete cds.
6236	ADR3	CC	CT	TT	HSU62961	Human succinyl CoA:3-oxoacid CoA transferase precursor (OXCT) mRNA, complete cds.
6482	CVD	AA	AG	GG	X69086	H.sapiens mRNA for utrophin
6498	CVD	AA	AG	GG	X71348	Homo sapiens vHNF1-C mRNA
6744	ADR5	CC	CT	TT	AC002310	Human Chromosome 16 BAC clone CIT987SK-A-635H12, complete sequence.
7133	CVD	CC	CG	GG	K02402	Human coagulation factor IX gene, complete cds.
8021	CVD	AA	AG	GG	Z13009	H.sapiens mRNA for E-cadherin

BAYSNP	SNP class	GTYP1 1	GTYP1 2	GTYP2 2	NCBI	DESCRIPTION
8060	CVD	AA	AG	GG	Z99572	Human DNA sequence from PAC 86F14 on chromosome 1q23-1q24. Contains coagulation factor V, ESTs and STS.
8210	EFF	AA	AG	GG	ABCB11	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11
8592	VEFF	CC	CT	TT	J04038	Human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene, complete cds.
8816	EFF	CC	CG	GG	L36033	Human pre-B cell stimulating factor homologue (SDF1b) mRNA, complete cds.
8846	CVD	AA	AG	GG	L41162	Homo sapiens collagen alpha 3 type IX (COL9A3) mRNA, complete cds.
8943	CVD	AA	AC	CC	AF050163	Homo sapiens lipoprotein lipase precursor, gene, partial cds.
9193	CVD	CC	CG	GG	M12674	Human estrogen receptor mRNA, complete cds.
9443	CVD	CC	CT	TT	U09587	Human glycyl-tRNA synthetase mRNA, complete cds.
9516	CVD	AA	AG	GG	U16720	Human interleukin 10 (IL10) gene, complete cds.
9698	ADR	AA	AG	GG	HS5211110	Homo sapiens X28 region near ALD locus containing dual specificity phosphatase 9 (DUSP9), ribosomal protein L18a (RPL18a), Ca2+/Calmodulin-dependent protein kinase I (CAMKI), creatine transporter (CRTTR), CDM protein (CDM), adrenoleukodystrophy protein (AL)

BAYSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE2	NCBI	DESCRIPTION
9698	ADR3	AA	AG	GG	HS5211110	Homo sapiens X28 region near ALD locus containing dual specificity phosphatase 9 (DUSP9), ribosomal protein L18a (RPL18a), Ca2+/Calmodulin-dependent protein kinase I (CAMKI), creatine transporter (CRTR), CDM protein (CDM), adrenoleukodystrophy protein (AL)
9698	EFF	AA	AG	GG	HS5211110	Homo sapiens X28 region near ALD locus containing dual specificity phosphatase 9 (DUSP9), ribosomal protein L18a (RPL18a), Ca2+/Calmodulin-dependent protein kinase I (CAMKI), creatine transporter (CRTR), CDM protein (CDM), adrenoleukodystrophy protein (AL)
9698	ADR5	AA	AG	GG	HS5211110	Homo sapiens X28 region near ALD locus containing dual specificity phosphatase 9 (DUSP9), ribosomal protein L18a (RPL18a), Ca2+/Calmodulin-dependent protein kinase I (CAMKI), creatine transporter (CRTR), CDM protein (CDM), adrenoleukodystrophy protein (AL)

BAYSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE2 2	NCBI	DESCRIPTION
9698	CVD	AA	AG	GG	HS5211110	Homo sapiens X28 region near ALD locus containing dual specificity phosphatase 9 (DUSP9), ribosomal protein L18a (RPL18a), Ca2+/Calmodulin-dependent protein kinase I (CAMKI), creatine transporter (CRTR), CDM protein (CDM), adrenoleukodystrophy protein (AL)
9849	CVD	CC	CT	null	X04588	Human 2.5 kb mRNA for cytoskeletal tropomyosin TM30(nm)
9883	CVD	AA	AG	GG	BC000140	PCCA: propionyl Coenzyme A carboxylase, alpha polypeptide
10079	CVD	AA	AG	GG	X77197	H.sapiens mRNA for chloride channel
10481	ADR5	AA	AT	TT	AF023268	Homo sapiens clk2 kinase (CLK2), propin1, cotel1, glucocerebro- sidase (GBA), and metaxin genes, complete cds; metaxin pseudogene and glucocerebrosidase pseudogene; and thrombospondin3 (THBS3) gene, partial cds.
10542	UEFF	CC	CT	TT	AF066859	Homo sapiens muscle glycogen phosphorylase (PYGM) mRNA, complete cds.
10542	ADR5	CC	CT	TT	AF066859	Homo sapiens muscle glycogen phosphorylase (PYGM) mRNA, complete cds.

BAVSNP	SNP class	GTYP1 1	GTYP1 2	GTYP1 2	NCBI	DESCRIPTION
10600	EFF	AA	AG	GG	AF129756	Homo sapiens MSH55 gene, partial cds; and CLIC1, DDAH, G6b, G6c, G5b, G6d, G6e, G6f, BAT5, G5b, CSK2B, BAT4, G4, Apo M, BAT3, BAT2, AIF-1, IC7, LST-1, LTB, TNF, and LTA genes, complete cds.
10621	CVD	CC	CT	TT	AF220490	Homo sapiens group III secreted phospholipase A2 mRNA, complete cds.
10745	ADR5	AA	AG	GG	D11456	Human mRNA for Xanthine dehydrogenase, complete cds.
10745	VEFF	AA	AG	GG	D11456	Human mRNA for Xanthine dehydrogenase, complete cds.
10747	ADR	CC	CT	TT	D11456	Human mRNA for Xanthine dehydrogenase, complete cds.
10747	CVD	CC	CT	TT	D11456	Human mRNA for Xanthine dehydrogenase, complete cds.
10747	ADR3	CC	CT	TT	D11456	Human mRNA for Xanthine dehydrogenase, complete cds.
10771	ADR5	CC	CG	GG	D37932	Human mRNA for HPC-1, partial cds.
10771	EFF	CC	CG	GG	D37932	Human mRNA for HPC-1, partial cds.
10870	CVD	AA	AG	GG	AH002776	LDLR: low density lipoprotein receptor (familial hypercholesterolemia)
10877	CVD	AA	AC	CC	AC005832	Homo sapiens 12p13.3 BAC RPC111-500M8 (Roswell Park Cancer Institute Human BAC Library) complete sequence.
10948	CVD	GG	GT	TT	M10065	Human apolipoprotein E (epsilon-4 allele) gene, complete cds.

BAYSNP	SNP class	CTYPE1 1	CTYPE1 2	CTYPE1 2	CTYPE2	NCBI	DESCRIPTION
11001	ADR5	CC	CT	TT	TT	M34424	Human acid alpha-glucosidase (GAA) mRNA, complete cds.
11073	ADR5	CC	CG	GG	GG	AF070670	Homo sapiens protein phosphatase 2C alpha 2 mRNA, complete cds.
11153	CVD	CC	CT	CT	TT	U57623	Human fatty acid binding protein FABP gene, complete cds.
11210	CVD	CC	CT	CT	TT	AB014460	Homo sapiens TSC2, NTHL1/NTH1 and SLC9A3R2/E3KARP genes, partial and complete cds.
11210	ADR3	CC	CT	CT	TT	AB014460	Homo sapiens TSC2, NTHL1/NTH1 and SLC9A3R2/E3KARP genes, partial and complete cds.
11210	ADR	CC	CT	CT	TT	AB014460	Homo sapiens TSC2, NTHL1/NTH1 and SLC9A3R2/E3KARP genes, partial and complete cds.
11248	ADR	CC	CT	CT	TT	X60435	H.sapiens gene PACAP for pituitary adenylate cyclase activating polypeptide
11248	CVD	CC	CT	CT	TT	X60435	H.sapiens gene PACAP for pituitary adenylate cyclase activating polypeptide
11372	CVD	AA	AG	GG	GG	Z82215	Human DNA sequence from clone RP1-68O2 on chromosome 22 Contains the 5' end of the APOL2 gene for apolipoprotein L 2, the APOL gene for apolipoprotein L, the MYH9 gene for nonmuscle type myosin heavy chain 9. ESTs, STSs and GSSs.
11449	CVD	CC	CG	GG	GG	AF050163	Homo sapiens lipoprotein lipase precursor, gene, partial cds.
11450	EFF	AA	AT	TT	TT	AF050163	Homo sapiens lipoprotein lipase precursor, gene, partial cds.

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DBSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE2 2	NCBI	DESCRIPTION
11470	CVD	CC	CT	null	AJ006945	Human P2Y1 gene
11472	CVD	AA	AT	null	AJ006945	Human P2Y1 gene
11487	ADR5	AT	TT	null	M75106	Human prepro-plasma carboxypeptidase B mRNA, complete cds.
11487	ADR3	AT	TT	null	M75106	Human prepro-plasma carboxypeptidase B mRNA, complete cds.
11488	ADR5	CC	CG	GG	M75106	Human prepro-plasma carboxypeptidase B mRNA, complete cds.
11488	UEFF	CC	CG	GG	M75106	Human prepro-plasma carboxypeptidase B mRNA, complete cds.
11488	ADR3	CC	CG	GG	M75106	Human prepro-plasma carboxypeptidase B mRNA, complete cds.
11493	CVD	AA	AG	GG	U03882	Human monocyte chemoattractant protein 1 receptor (MCP-1RA) alternatively spliced mRNA, complete cds.
11502	ADR3	CC	CT	TT	U58917	Homo sapiens IL-17 receptor mRNA, complete cds.
11502	ADR5	CC	CT	TT	U58917	Homo sapiens IL-17 receptor mRNA, complete cds.
11534	CVD	GG	GT	null	AJ276102	Homo sapiens mRNA for GPRC5C protein

BAYSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE2 2	NCBI	DESCRIPTION
11537	CVD	AA	AG	GG	AL022721	Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome Proliferato
11537	EFF	AA	AG	GG	AL022721	Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome Proliferato
11560	EFF	AA	AG	GG	AC006312	Homo sapiens chromosome 9, clone hRPK.401_G_18, complete sequence.
11578	CVD	CC	CT	null	AC073593	Homo sapiens 12 BAC RP11-13J12 (Roswell Park Cancer Institute Human BAC Library) complete sequence.
11594	ADR3	CC	CT	TT	AF026069	Homo sapiens phosphomevalonate kinase (HUMPMKI) gene, partial cds.
11594	ADR5	CC	CT	TT	AF026069	Homo sapiens phosphomevalonate kinase (HUMPMKI) gene, partial cds.
11594	CVD	CC	CT	TT	AF026069	Homo sapiens phosphomevalonate kinase (HUMPMKI) gene, partial

BAVSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE1 2	GTTYPE2	NCBI	DESCRIPTION
11594	ADR	CC	CT	TT	AF026069		cds. Homo sapiens phosphomevalonate kinase (HUMPMKI) gene, partial cds.
11624	CVD	CC	CT	TT	AL022721		Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome Proliferato
11624	EFF	CC	CT	TT	AL022721		Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome Proliferato
11627	CVD	CC	CT	TT	AL022721		Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome Proliferator
11627	EFF	CC	CT	TT	AL022721		Human DNA sequence from clone 109F14 on chromosome 6p21.2-

BAYSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE1 2	GTTYPE2	NCBI	DESCRIPTION
							21.3. Contains the alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome Proliferato
11644	ADR5	AA	AG	AG	GG	D84371	Homo sapiens mRNA for serum aryldiacylphosphatase, complete cds.
11650	EFF	AA	AG	AG	GG	X56668	Human DNA for calretinin exon 1
11654	ADR5	AA	AG	AG	GG	AJ276180	Homo sapiens partial ZNF202 gene for zinc finger protein homolog, exon 4
11654	ADR3	AA	AG	AG	GG	AJ276180	Homo sapiens partial ZNF202 gene for zinc finger protein homolog, exon 4
11655	ADR5	AA	AC	AC	CC	AJ276180	Homo sapiens partial ZNF202 gene for zinc finger protein homolog, exon 4
11655	ADR3	AA	AC	AC	CC	AJ276180	Homo sapiens partial ZNF202 gene for zinc finger protein homolog, exon 4
11656	CVD	CC	CT	CT	TT	NM_001081	CUBN: cubilin (intrinsic factor-cobalamin receptor)
11656	EFF	CC	CT	CT	TT	NM_001081	CUBN: cubilin (intrinsic factor-cobalamin receptor)
11825	ADR5	AA	AG	AG	null	AC008897	Homo sapiens chromosome 5 clone CTD-2235C13, WORKING DRAFT SEQUENCE, 6 ordered pieces.
11914	ADR5	AA	AT	AT	TT	AF030555	Homo sapiens acyl-CoA synthetase 4 (ACS4) mRNA, complete cds.

BAVSNP	SNP class	GTTYPE1 1	GTTYPE1 2	GTTYPE2	NCBI	DESCRIPTION
12008	EFF	CC	CT	null	AF107885	Homo sapiens chromosome 14q24.3 clone BAC270M14 transforming growth factor-beta 3 (TGF-beta 3) gene, complete cds; and unknown genes.
12008	ADR5	CC	CT	null	AF107885	Homo sapiens chromosome 14q24.3 clone BAC270M14 transforming growth factor-beta 3 (TGF-beta 3) gene, complete cds; and unknown genes.
12097	ADR5	AG	GG	null	AF280107	Homo sapiens cytochrome P450 polypeptide 43 (CYP3A43) gene, partial cds; cytochrome P450 polypeptide 4 (CYP3A4) and cytochrome P450 polypeptide 7 (CYP3A7) genes, complete cds; and cytochrome P450 polypeptide 5 (CYP3A5) gene, partial cds.
12097	ADR3	AG	GG	null	AF280107	Homo sapiens cytochrome P450 polypeptide 43 (CYP3A43) gene, partial cds; cytochrome P450 polypeptide 4 (CYP3A4) and cytochrome P450 polypeptide 7 (CYP3A7) genes, complete cds; and cytochrome P450 polypeptide 5 (CYP3A5) gene, partial cds.
12366	UEFF	AA	AG	GG	D63807	Human mRNA for lanosterol synthase, complete cds.
12366	ADR5	AA	AG	GG	D63807	Human mRNA for lanosterol synthase, complete cds.
12619	ADR5	AG	GG	null	L13744	Human AF-9 mRNA, complete cds.
13025	ADR5	AA	AC	CC	M85168	Human glycogen debranching enzyme mRNA, complete cds.
13191	CVD	AA	AG	GG	HSHMGCOAS	H.sapiens mRNA for 3-hydroxy-3-methylglutaryl coenzyme A

BAYSNP	SNP class	GTYP1 1	GTYP1 2	GTYP1 2	GTYP2 2	NCBI	DESCRIPTION
							synthase
13937	ADR5	AA	AC	CC		M68840	Human monoamine oxidase A (MAOA) mRNA, complete cds.
900002	CVD	GG	GT	TT		AF192304	Homo sapiens vHNF1-C mRNA
900013	CVD	CC	CG	GG		L05628	Human multidrug resistance-associated protein mRNA
900025	CVD	GG	GT	TT		Z22535	ALK3
900032	CVD	CC	CT	TT		af096786	GPR-55
900045	EFF	CC	CT	TT		X63432	H.sapiens ACTB mRNA for mutant beta-actin
900065	CVD	AA	AC	CC		AC009245	Homo sapiens chromosome 7 clone RP11-351B12, complete sequence
900078	ADR3	AA	AG	GG		NM_017460	CYP3A4
900078	ADR5	AA	AG	GG		NM_017460	CYP3A4
900082	ADR3	AA	AG	GG		NM_002489	NADH dehydrogenase (ubiquinone) 1, alpha subcomplex, 4 (9kD, MLRQ), NDUFA4
900082	ADR5	AA	AG	GG		NM_002489	NADH dehydrogenase (ubiquinone) 1, alpha subcomplex, 4 (9kD, MLRQ), NDUFA4
900096	CVD	AA	AG	GG		NM_003376	VEGF
900107	ADR5	CC	CT	TT		NM_033013	nuclear receptor subfamily 1, group I, member 2 (NR1I2)
900115	ADR5	AA	AG	GG		ATP2A1	ATPase, Ca++ transporting, cardiac muscle, fast twitch 1

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BAYSNP	SNP class	GTYP1 1	GTYP1 2	GTYP1 2	GTYP2	NCBI	DESCRIPTION
900115	EFF	AA	AG	AG	GG	ATP2A1	ATPase, Ca++ transporting, cardiac muscle, fast twitch 1
900121	ADR	GG	GT	GT	TT	NM_016156	MTMR2 myotubularin related protein 2 (MTMR2)
900173	CVD	GG	GT	GT	TT	M76722	LPL: lipoprotein lipase
10000002	EFF	AA	AG	AG	GG	M32992	Cholesteryl ester transfer protein (CETP)
10000006	CVD	AA	AG	AG	GG	NM_000384	Apolipoprotein B
10000014	CVD	AA	AC	AC	CC	M61888	E-Selectin (CD62E)
10000025	CVD	CC	CT	CT	TT	AC073593	Scavenger receptor class B type I

Table 4 Cohorts

Given are names (as used in table 5) and formations of the various cohorts that were used for genotyping

COHORT	Definition
HELD_ALL_GOOD/BAD	Healthy elderly individuals of both genders with good or bad serum lipid profiles (as defined in table 1a)
HELD_FEM_GOOD/BAD	Healthy elderly individuals (female) with good or bad serum lipid profiles (as defined in table 1a)
HELD_MAL_GOOD/BAD	Healthy elderly individuals (male) with good or bad serum lipid profiles (as defined in table 1a)
CVD_ALL_CASE/CTRL	Individuals with diagnosis of cardiovascular disease and healthy controls (both genders)
CVD_FEM_CASE/CTRL	Individuals with diagnosis of cardiovascular disease and healthy controls (female)
CVD_MAL_CASE/CTRL	Individuals with diagnosis of cardiovascular disease and healthy controls (male)
HELD_FEM_ADRCTRL	Female individuals that tolerate administration of cerivastatin without exhibiting signs of ADR (as defined in table 1b)
HELD_FEM_ADRCASE	Female individuals that exhibited ADR (as defined in table 1b) upon administration of cerivastatin
HELD_MAL_ADRCTRL	Male individuals that tolerate administration of cerivastatin without exhibiting signs of ADR (as defined in table 1b)
HELD_MAL_ADRCASE	Male individuals that exhibited ADR (as defined in table 1b) upon administration of cerivastatin
HELD_ALL_ADRCTRL	Individuals of both genders that tolerate administration of cerivastatin without exhibiting signs of ADR (as defined in table 1b)
HELD_ALL_ADRCASE	Individuals of both genders that exhibited ADR (as defined in table 1b) upon administration of cerivastatin
HELD_FEM_LORESP	Female individuals with a minor response to cerivastatin administration (as defined in table 1b)
HELD_FEM_HIRES	Female individuals with a high response to cerivastatin administration (as defined in table 1b)
HELD_FEM_HIHDL/LOHDL	Healthy elderly individuals (female) with high or low serum HDL cholesterol levels (as defined in table 1c)
HELD_MAL_HIHDL/LOHDL	Healthy elderly individuals (male) with high or low serum HDL cholesterol levels (as defined in table 1c)
HELD_ALL_HIHDL/LOHDL	Healthy elderly individuals of both genders with high or low serum HDL cholesterol levels (as defined in table 1c)
HELD_FEM_ADR3CASE	Female individuals that exhibited advanced ADR (as defined in table 1b) upon administration of cerivastatin
HELD_MAL_ADR3CASE	Male individuals that exhibited advanced ADR (as defined in table 1b) upon administration of cerivastatin
HELD_ALL_ADR3CASE	Individuals of both genders that exhibited advanced ADR (as defined in table 1b) upon administration of cerivastatin

COHORT	Definition
HELD_FEM_VLORESP	Female individuals with a very low response to cerivastatin administration (as defined in table 1b)
HELD_FEM_VHIRESP	Female individuals with a very high response to cerivastatin administration (as defined in table 1b)
HELD_FEM_ADR5CASE	Female individuals that exhibited severe ADR (as defined in table 1b) upon administration of cerivastatin
HELD_MAL_ADR5CASE	Male individuals that exhibited severe ADR (as defined in table 1b) upon administration of cerivastatin
HELD_ALL_ADR5CASE	Individuals of both genders that exhibited severe ADR (as defined in table 1b) upon administration of cerivastatin
HELD_FEM_ULORESP	Female individuals with a ultra low response to cerivastatin administration (as defined in table 1b)
HELD_FEM_UHIRESP	Female individuals with a ultra high response to to cerivastatin administration (as defined in table 1b)

Table 5a and 5b Cohort sizes and p-values of PA SNPs

The baySNP number refers to an internal numbering of the PA SNPs. Cpval denotes the classical Pearson chi-squared test, Xpval denotes the exact version of Pearson's chi-squared test, LRpval denotes the likelihood-ratio chi-squared test, Cpvalue, Xpvalue, and LRpvalue are calculated as described in (SAS/STAT User's Guide of the SAS OnlineDoc, Version 8), (L. D. Fisher and G. van Belle, Biostatistics, Wiley Interscience 1993), and (A. Agresti, Statistical Science 7, 131 (1992)). The GTYPE and Allele p values were obtained through the respective chi square tests when comparing COHORTs A and B. For GTYPE p value the number of patients in cohort A carrying genotypes 11, 12 or 22 (FQ11 A, FQ 12 A, FQ 22 A; genotypes as defined in table 3) were compared with the respective patients in cohort B (FQ11 B, FQ 12 B, FQ 22 B; genotypes as defined in table 3) resulting in the respective chi square test with a 3x2 matrix. For Allele p values we compared the allele count of alleles 1 and 2 (A1 and A2) in cohorts A and B, respectively (chi square test with a 2x2 matrix). SIZE A and B: Number of patients in cohorts A and B, respectively. See table 4 for definition of COHORTs A and B.

Table 5a

LTYSNP	AT	AT2	COHORTA	SIZE	FQ1A	FQ2A	FQM	FQ1A	FQ2A	COHORTB	SIZE	FQ1B	FQ2B	FQM	FQ1B	FQ2B
				A			A				B			B		
28	C	T	HELD_FEM_HIRES	12	4	20	1	2	9	HELD_FEM_LORESP	22	18	26	3	12	7
29	A	G	HELD_ALL_LOHDL	10	12	8	4	4	2	HELD_ALL_HIHDL	15	7	23	0	7	8
29	A	G	HELD_MAL_ADRCASE3ULN	26	33	19	13	7	6	HELD_MAL_ADRCTRL	72	68	76	18	32	22
29	A	G	HELD_MAL_ADRCASE5ULN	9	13	5	5	3	1	HELD_MAL_ADRCTRL	72	68	76	18	32	22
52	C	G	HELD_FEM_HIRES	18	24	12	7	10	1	HELD_FEM_LORESP	31	27	35	5	17	9
56	A	G	HELD_FEM_HIRES	12	5	19	0	5	7	HELD_FEM_LORESP	22	2	42	0	2	20
89	A	G	HELD_ALL_CASE	45	90	0	45	0	0	HELD_ALL_CTRL	40	77	3	37	3	0
90	C	T	HELD_FEM_CASE	31	29	33	8	13	10	HELD_FEM_CTRL	22	27	17	6	15	1
99	C	T	HELD_FEM_BAD	82	54	110	13	28	41	HELD_FEM_GOOD	80	51	109	5	41	34
140	C	T	HELD_FEM_HIRES	12	24	0	0	0	12	HELD_FEM_LORESP	21	4	38	1	2	18
152	A	G	HELD_FEM_HIRES	12	12	12	3	6	3	HELD_FEM_LORESP	22	33	11	12	9	1
214	A	G	HELD_ALL_BAD	97	156	38	59	38	0	HELD_ALL_GOOD	113	182	44	73	36	4
214	A	G	HELD_FEM_BAD	81	131	31	50	31	0	HELD_FEM_GOOD	78	122	34	48	26	4
221	C	G	HELD_ALL_CASE	45	26	64	7	12	26	HELD_ALL_CTRL	39	27	51	3	21	15
221	C	G	HELD_FEM_CASE	31	17	45	4	9	18	HELD_FEM_CTRL	22	18	26	2	14	6
224	C	T	HELD_FEM_BAD	79	110	48	51	8	20	HELD_FEM_GOOD	79	125	33	60	5	14
224	C	T	HELD_MAL_BAD	20	35	5	17	1	2	HELD_MAL_GOOD	37	51	23	25	1	11
294	C	T	HELD_ALL_CASE	45	56	34	16	24	5	HELD_ALL_CTRL	40	58	22	18	22	0
307	C	T	CVD_FEM_CASE	36	19	53	2	15	19	CVD_FEM_CTRL	38	38	38	9	20	9
307	C	T	HELD_ALL_BAD	102	70	134	0	70	32	HELD_ALL_GOOD	117	63	171	0	63	54
411	A	T	HELD_ALL_LOHDL	10	17	3	7	3	0	HELD_ALL_HIHDL	15	18	12	5	8	2
449	C	G	HELD_MAL_BAD	20	3	37	0	3	17	HELD_MAL_GOOD	37	16	58	1	14	22

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STSNP	AI/A2	COHORT A	SIZE A	FO1A	FO2A	FOH A	FO12 A	FO22 A	COHORT B	SIZE B	FO1B	FO2B	FO11 B	FO12 B	FO22 B
466	C T	CVD_FEM_CASE	35	27	43	6	15	14	CVD_FEM_CTRL	40	44	36	12	20	8
472	A G	HELD_FEM_HIRES	11	22	0	0	0	11	HELD_FEM_LORESP	22	12	32	3	6	13
542	A G	HELD_MAL_CASE	14	12	16	2	8	4	HELD_MAL_CTRL	19	2	36	0	2	17
542	A G	HELD_MAL_LOHDL	21	14	28	3	8	10	HELD_MAL_HIHDL	27	3	51	0	3	24
542	A G	HELD_ALL_ADRCASE	159	53	265	0	53	106	HELD_ALL_ADRCtrl	154	37	271	2	33	119
542	A G	HELD_FEM_LOHDL	23	2	44	0	2	21	HELD_FEM_HIHDL	32	10	54	1	8	23
739	C G	HELD_ALL_CASE	45	39	51	9	21	15	HELD_ALL_CTRL	40	48	32	14	20	6
821	A C	HELD_MAL_BAD2	309	180	438	32	116	161	HELD_MAL_GOOD2	349	174	524	18	138	193
821	A C	HELD_FEM_VHIRES	10	4	16	0	4	6	HELD_FEM_VLORESP	14	14	14	4	6	4
1005	A G	HELD_MAL_CASE	14	26	2	12	2	0	HELD_MAL_CTRL	18	27	9	11	5	2
1055	A T	HELD_MAL_CASE	9	3	15	0	3	6	HELD_MAL_CTRL	12	8	16	4	0	8
1056	A G	HELD_FEM_HIRES	24	30	18	12	6	6	HELD_FEM_LORESP	33	41	25	10	21	2
1085	A G	HELD_MAL_BAD	20	17	23	3	11	6	HELD_MAL_GOOD	36	46	26	15	16	5
1085	A G	CVD_FEM_CASE	34	51	17	20	11	3	CVD_FEM_CTRL	40	47	33	16	15	9
1086	A G	HELD_MAL_BAD	20	24	16	7	10	3	HELD_MAL_GOOD	36	28	44	5	18	13
1092	C G	HELD_MAL_BAD	20	9	31	2	5	13	HELD_MAL_GOOD	37	29	45	4	21	12
1096	G T	HELD_MAL_CASE	14	7	21	0	7	7	HELD_MAL_CTRL	18	3	33	0	3	15
1096	G T	CVD_MAL_CASE	69	21	117	4	13	52	CVD_MAL_CTRL	33	12	54	0	12	21
1101	C T	HELD_FEM_HIRES	12	24	0	12	0	0	HELD_FEM_LORESP	22	40	4	18	4	0
1204	A G	HELD_MAL_BAD	19	12	26	2	8	9	HELD_MAL_GOOD	35	9	61	0	9	26
1204	A G	HELD_ALL_BAD	99	62	136	12	38	49	HELD_ALL_GOOD	115	52	178	8	36	71
1504	C T	HELD_ALL_CASE	44	37	51	5	27	12	HELD_ALL_CTRL	39	36	42	12	12	15
1504	C T	HELD_MAL_BAD	19	12	26	0	12	7	HELD_MAL_GOOD	37	33	41	8	17	12
1504	C T	HELD_MAL_CASE	14	13	15	2	9	3	HELD_MAL_CTRL	18	12	24	4	4	10
1504	C T	HELD_FEM_CASE	30	24	36	3	18	9	HELD_FEM_CTRL	21	24	18	8	8	5
1511	G T	HELD_FEM_HIRES	12	15	9	3	9	0	HELD_FEM_LORESP	22	35	9	14	7	1

BYSNP	M1A2	COHORTA	SIZE A1	TQ1A	TQ1A A	TQ1A B	FQ1A	FQ1A A	FQ1A B	FQ12 A	FQ12 A	FQ12 B	COHORTB	SIZE B	FQ1B	FQ2B	FQ11 B	FQ12 B	FQ23 B
1524	A	C	HELD_FEM_ADRCASE3ULN	38	16	60	0	16	22	HELD_FEM_ADRCTRL	82	39	125	8	23	51			
1556	C	G	HELD_FEM_HIRES	12	7	17	0	7	5	HELD_FEM_LORESP	22	3	41	0	3	19			
1561	A	C	CVD_FEM_CASE	36	58	14	23	12	1	CVD_FEM_CTRL	40	53	27	17	19	4			
1582	C	T	HELD_MAL_BAD	20	5	35	0	5	15	HELD_MAL_GOOD	37	22	52	5	12	20			
1638	A	G	HELD_FEM_CASE	31	10	52	1	8	22	HELD_FEM_CTRL	22	15	29	2	11	9			
1653	G	T	CVD_MAL_CASE	69	70	68	15	40	14	CVD_MAL_CTRL	33	30	36	10	10	13			
1662	C	T	HELD_MAL_CASE	14	8	20	4	0	10	HELD_MAL_CTRL	18	36	0	0	0	18			
1714	A	G	CVD_MAL_CASE	66	32	100	3	26	37	CVD_MAL_CTRL	34	26	42	6	14	14			
1722	C	T	HELD_FEM_ADRCASE5ULN	18	21	15	8	5	5	HELD_FEM_ADRCTRL	81	71	91	14	43	24			
1757	A	G	HELD_FEM_HIRES	20	15	25	4	7	9	HELD_FEM_LORESP	32	16	48	0	16	16			
1765	A	G	HELD_ALL_ADRCASE3ULN	63	9	117	1	7	55	HELD_ALL_ADRCTRL	149	56	242	4	48	97			
1765	A	G	HELD_ALL_ADRCASE3ULN	63	9	117	1	7	55	HELD_ALL_ADRCTRL	149	56	242	4	48	97			
1765	A	G	HELD_ALL_ADRCASE5ULN	27	3	51	0	3	24	HELD_ALL_ADRCTRL	149	56	242	4	48	97			
1765	A	G	HELD_ALL_ADRCASE5ULN	27	3	51	0	3	24	HELD_ALL_ADRCTRL	149	56	242	4	48	97			
1765	A	G	HELD_MAL_ADRCASE3ULN	26	2	50	0	2	24	HELD_MAL_ADRCTRL	70	25	115	2	21	47			
1765	A	G	HELD_MAL_ADRCASE3ULN	26	2	50	0	2	24	HELD_MAL_ADRCTRL	70	25	115	2	21	47			
1765	A	G	HELD_MAL_ADRCASE5ULN	10	20	0	0	0	10	HELD_MAL_ADRCTRL	70	25	115	2	21	47			
1765	A	G	HELD_MAL_ADRCASE5ULN	10	20	0	0	0	10	HELD_MAL_ADRCTRL	70	25	115	2	21	47			
1765	A	G	HELD_FEM_ADRCASE3ULN	37	7	67	1	5	31	HELD_FEM_ADRCTRL	79	31	127	2	27	50			
1765	A	G	HELD_FEM_ADRCASE3ULN	37	7	67	1	5	31	HELD_FEM_ADRCTRL	79	31	127	2	27	50			
1776	A	G	HELD_ALL_CASE	45	90	0	45	0	0	HELD_ALL_CTRL	40	74	6	37	0	3			
1776	A	G	HELD_FEM_CASE	31	62	0	31	0	0	HELD_FEM_CTRL	22	40	4	20	0	2			
1799	C	T	HELD_FEM_BAD2	291	365	217	123	119	49	HELD_FEM_GOOD2	356	468	244	145	178	33			
1799	C	T	HELD_MAL_CASE	14	15	13	4	7	3	HELD_MAL_CTRL	18	28	8	11	6	1			
1806	A	G	HELD_FEM_HIRES	12	23	1	11	1	0	HELD_FEM_LORESP	22	34	10	14	6	2			
1837	C	T	HELD_FEM_BAD2	304	436	172	164	108	32	HELD_FEM_GOOD2	355	499	211	166	167	22			

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DaySNP	AltA2	CohortA	Size	FQ1A	FQ2A	FQ1A	FQ2A	FQ1A	FQ2A	CohortB	Size	FQ1B	FQ2B	FQ1B	FQ2B	FQ12	FQ22
			A			A		A			B	B		B		B	
1837	C T	HELD_ALL_BAD2	607	891	323	334	223	50	HELD_ALL_GOOD2	682	952	412	322	308	52		
1837	C T	HELD_ALL_ADRCASE3ULN	28	46	10	20	6	2	HELD_ALL_ADRCTRL	155	208	102	66	76	13		
1837	C T	HELD_MAL_ADRCASE	77	107	47	37	33	7	HELD_MAL_ADRCTRL	72	86	58	21	44	7		
1837	C T	HELD_MAL_BAD2	303	455	151	170	115	18	HELD_MAL_GOOD2	327	453	201	156	141	30		
1870	C T	HELD_ALL_CASE	45	29	61	2	25	18	HELD_ALL_CTRL	39	16	62	3	10	26		
1870	C T	HELD_FEM_CASE	31	22	40	1	20	10	HELD_FEM_CTRL	22	9	35	1	7	14		
1882	C T	CVD_MAL_CASE	69	79	59	21	37	11	CVD_MAL_CTRL	34	43	25	9	25	0		
1988	C T	HELD_ALL_BAD	100	143	57	52	39	9	HELD_ALL_GOOD	116	144	88	48	48	20		
2000	C T	CVD_MAL_CASE	70	136	4	68	2	0	CVD_MAL_CTRL	34	58	10	29	5	0		
2000	C T	CVD_ALL_CASE	105	202	8	101	4	0	CVD_ALL_CTRL	74	130	18	65	9	0		
2000	C T	HELD_FEM_CASE2	46	90	2	45	1	0	HELD_FEM_CTRL2	42	74	10	37	5	0		
2000	C T	HELD_MAL_LOHDL	20	40	0	20	0	0	HELD_MAL_HIHDL	22	40	4	20	2	0		
2000	C T	HELD_FEM_ADRCASE	79	154	4	77	2	0	HELD_FEM_ADRCTRL	82	152	12	76	6	0		
2000	C T	HELD_MAL_CASE	14	22	6	11	3	0	HELD_MAL_CTRL	19	36	2	18	1	0		
2071	A G	CVD_ALL_CASE	102	80	124	14	52	36	CVD_ALL_CTRL	74	42	106	4	34	36		
2078	G T	HELD_MAL_BAD	18	13	23	1	11	6	HELD_MAL_GOOD	35	13	57	0	13	22		
2085	G T	HELD_FEM_VHIRESP	10	16	4	6	4	0	HELD_FEM_VLORESP	14	13	15	3	7	4		
2095	A G	CVD_ALL_CASE	105	4	206	4	101	0	CVD_ALL_CTRL	73	146	0	0	73	0		
2119	A G	HELD_MAL_BAD	20	23	17	3	17	0	HELD_MAL_GOOD	37	53	21	16	21	0		
2119	A G	HELD_ALL_BAD	102	131	73	29	73	0	HELD_ALL_GOOD	117	166	68	49	68	0		
2119	A G	HELD_FEM_HIRES	12	15	9	3	9	0	HELD_FEM_LORESP	22	35	9	13	9	0		
2141	A G	HELD_FEM_HIRES	12	6	18	0	6	6	HELD_FEM_LORESP	22	6	38	2	2	18		
2141	A G	HELD_ALL_CASE	45	17	73	0	17	28	HELD_ALL_CTRL	39	15	63	3	9	27		
2182	A G	HELD_FEM_HIRES	12	18	6	6	6	0	HELD_FEM_LORESP	21	16	26	1	14	6		
2234	G T	HELD_MAL_BAD	20	10	30	0	10	10	HELD_MAL_GOOD	35	32	38	7	18	10		
2281	A C	HELD_FEM_VHIRESP	9	5	13	0	5	4	HELD_FEM_VLORESP	13	15	11	4	7	2		

BYSNP	AN	AN2	CÓHORTA	SIZE A	FO2A	FO1A	FO2B	FO1B	SIZE B	CÓHORTB	FO22 A	FO12 A	FO22 B	FO12 B	FO22 B			
2298	A	C	CVD_FEM_CASE	35	18	52	4	10	21	CVD_FEM_CTRL			38	20	56	0	20	18
2298	A	C	HELD_MAL_CASE2	29	8	50	0	8	21	HELD_MAL_CTRL2			28	16	40	2	12	14
2341	C	T	HELD_FEM_CASE	31	6	56	0	6	25	HELD_FEM_CTRL			22	44	0	0	0	22
2357	A	G	HELD_ALL_CASE2	74	28	120	5	18	51	HELD_ALL_CTRL2			71	25	117	0	25	46
2357	A	G	HELD_ALL_CASE	45	16	74	4	8	33	HELD_ALL_CTRL			40	14	66	0	14	26
2357	A	G	HELD_MAL_BAD	20	4	36	0	4	16	HELD_MAL_GOOD			36	17	55	0	17	19
2357	A	G	HELD_FEM_CASE	31	12	50	4	4	23	HELD_FEM_CTRL			22	7	37	0	7	15
2366	G	T	CVD_FEM_CASE	33	38	28	12	14	7	CVD_FEM_CTRL			40	31	49	8	15	17
2423	A	G	CVD_FEM_CASE	33	45	21	16	13	4	CVD_FEM_CTRL			39	38	40	12	14	13
2708	C	T	CVD_FEM_CASE	29	57	1	28	1	0	CVD_FEM_CTRL			40	73	7	33	7	0
2995	A	C	HELD_FEM_ADRCASE5ULN	18	16	20	3	10	5	HELD_FEM_ADRCTRL			82	45	119	4	37	41
2995	A	C	HELD_FEM_UHIRESP	54	24	84	2	20	32	HELD_FEM_ULORESP			75	50	100	5	40	30
3360	G	T	HELD_MAL_ADRCASE5ULN	10	20	0	10	0	0	HELD_MAL_ADRCTRL			73	122	24	50	22	1
3464	A	G	HELD_ALL_CASE	45	21	69	3	15	27	HELD_ALL_CTRL			40	35	45	9	17	14
3464	A	G	HELD_FEM_CASE	31	13	49	3	7	21	HELD_FEM_CTRL			22	19	25	5	9	8
3689	C	G	HELD_FEM_HIRES	6	9	3	3	3	0	HELD_FEM_LORESP			14	10	18	1	8	5
3975	A	C	HELD_FEM_UHIRESP	56	28	84	2	24	30	HELD_FEM_ULORESP			75	58	92	10	38	27
3976	A	G	HELD_FEM_UHIRESP	56	28	84	2	24	30	HELD_FEM_ULORESP			75	57	93	11	35	29
4206	A	T	HELD_FEM_ADRCASE3ULN	37	36	38	8	20	9	HELD_FEM_ADRCTRL			83	103	63	31	41	11
4838	A	G	HELD_FEM_VHIRESP	10	16	4	7	2	1	HELD_FEM_VLORESP			14	14	14	3	8	3
4838	A	G	HELD_FEM_VHIRESP	10	16	4	7	2	1	HELD_FEM_VLORESP			14	14	14	3	8	3
4838	A	G	HELD_FEM_VHIRESP	10	16	4	7	2	1	HELD_FEM_VLORESP			14	14	14	3	8	3
4912	A	G	HELD_FEM_HIRES	12	14	10	7	0	5	HELD_FEM_LORESP			20	12	28	5	2	13
4925	A	C	HELD_MAL_CASE	14	21	7	7	7	0	HELD_MAL_CTRL			18	33	3	15	3	0
4966	A	G	HELD_MAL_ADRCASE3ULN	26	22	30	7	8	11	HELD_MAL_ADRCTRL			72	77	67	18	41	13
5014	A	G	HELD_ALL_ADRCASE5ULN	28	8	48	3	2	23	HELD_ALL_ADRCTRL			152	77	227	10	57	85

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INSNP	AT1A2	COHORT A	SIZE A	FO1A	FO2A	FO1A	FO2A	FO1A	FO2A	COHORT B	SIZE B	FO1B	FO2B	FO1B	FO2B	FO12	FO22
			A			A		A			B			B		B	B
5014	A G	HELD_FEM_ADRCASE5ULN	18	5	31	2	1	15		HELD_FEM_ADRCTRL	81	37	125	5	27		49
5296	A G	CVD_FEM_CASE	36	10	62	0	10	26		CVD_FEM_CTRL	40	4	76	0	4		36
5296	A G	HELD_FEM_HIRES	12	3	21	1	1	10		HELD_FEM_LORESP	22	9	35	0	9		13
5296	A G	CVD_ALL_CASE	104	27	181	1	25	78		CVD_ALL_CTRL	74	10	138	0	10		64
5298	C T	HELD_FEM_HIRES	11	3	19	1	1	9		HELD_FEM_LORESP	22	9	35	0	9		13
5298	C T	CVD_ALL_CASE	101	28	174	3	22	76		CVD_ALL_CTRL	74	10	138	0	10		64
5298	C T	CVD_FEM_CASE	35	10	60	1	8	26		CVD_FEM_CTRL	40	4	76	0	4		36
5320	A G	HELD_FEM_HIRES	19	12	26	1	10	8		HELD_FEM_LORESP	33	37	29	9	19		5
5361	A C	CVD_MAL_CASE	64	53	75	24	5	35		CVD_MAL_CTRL	32	36	28	18	0		14
5457	A G	HELD_FEM_HIRES	12	2	22	1	0	11		HELD_FEM_LORESP	21	8	34	1	6		14
5704	C T	HELD_MAL_BAD	20	10	30	1	8	11		HELD_MAL_GOOD	37	32	42	3	26		8
5704	C T	CVD_MAL_CASE	68	40	96	5	30	33		CVD_MAL_CTRL	33	30	36	6	18		9
5717	A G	HELD_FEM_ADRCASE3ULN	38	50	26	17	16	5		HELD_FEM_ADRCTRL	83	83	83	21	41		21
5717	A G	HELD_ALL_ADRCASE3ULN	65	74	56	21	32	12		HELD_ALL_ADRCTRL	156	144	168	34	76		46
5959	A G	HELD_ALL_CASE	43	52	34	16	20	7		HELD_ALL_CTRL	38	29	47	4	21		13
5959	A G	CVD_FEM_CASE	9	12	6	4	4	1		CVD_FEM_CTRL	13	7	19	0	7		6
5959	A G	HELD_MAL_CASE	14	15	13	4	7	3		HELD_MAL_CTRL	17	10	24	0	10		7
5959	A G	HELD_MAL_ADRCASE5ULN	9	6	12	2	2	5		HELD_MAL_ADRCTRL	67	67	67	13	41		13
5959	A G	HELD_FEM_ADRCASE	72	71	73	15	41	16		HELD_FEM_ADRCTRL	68	51	85	11	29		28
6162	C G	HELD_ALL_ADRCASE3ULN	64	37	91	1	35	28		HELD_ALL_ADRCTRL	151	90	212	19	52		80
6162	C G	HELD_ALL_ADRCASE	156	88	224	6	76	74		HELD_ALL_ADRCTRL	151	90	212	19	52		80
6162	C G	HELD_ALL_ADRCASE5ULN	27	16	38	0	16	11		HELD_ALL_ADRCTRL	151	90	212	19	52		80
6162	C G	HELD_MAL_ADRCASE3ULN	26	13	39	0	13	13		HELD_MAL_ADRCTRL	71	43	99	11	21		39
6162	C G	HELD_FEM_ADRCASE5ULN	18	13	23	0	13	5		HELD_FEM_ADRCTRL	80	47	113	8	31		41
6162	C G	HELD_MAL_ADRCASE	74	40	108	3	34	37		HELD_MAL_ADRCTRL	71	43	99	11	21		39
6236	C T	HELD_ALL_ADRCASE5ULN	27	24	30	6	12	9		HELD_ALL_ADRCTRL	152	84	220	13	58		81

laysnp	AI_A2	COHORT_A	SIZE	FOIA	FOZA	FOH	FOE2	COHORT_B	SIZE	FOIB	FO3B	FO1I	FOE2
			A			A	A		B			B	B
6236	C T	HELD_MAL_ADRCASE3ULN	27	23	31	4	15	HELD_MAL_ADRCTRL	72	38	106	5	28
6236	C T	HELD_MAL_ADRCASE5ULN	10	10	10	2	6	HELD_MAL_ADRCTRL	72	38	106	5	28
6236	C T	HELD_ALL_ADRCASE3ULN	63	47	79	10	27	HELD_ALL_ADRCTRL	152	84	220	13	58
6482	A G	HELD_MAL_LOHDL	17	18	16	5	8	HELD_MAL_HIHDL	21	34	8	15	4
6482	A G	HELD_ALL_BAD2	619	918	320	340	238	HELD_ALL_GOOD2	709	1098	320	436	226
6482	A G	HELD_MAL_CASE2	27	43	11	18	7	HELD_MAL_CTRL2	28	32	24	10	12
6482	A G	HELD_MAL_BAD2	309	461	157	173	115	HELD_MAL_GOOD2	339	539	139	220	99
6498	A G	CVD_FEM_CASE	32	60	4	28	4	CVD_FEM_CTRL	35	57	13	25	7
6744	C T	HELD_ALL_ADRCASE5ULN	26	21	31	4	13	HELD_ALL_ADRCTRL	149	74	224	9	56
7133	C G	HELD_MAL_CASE	14	20	8	10	0	HELD_MAL_CTRL	18	36	0	18	0
8021	A G	CVD_FEM_CASE	28	35	21	8	19	CVD_FEM_CTRL	36	44	28	15	14
8060	A G	CVD_FEM_CASE	35	65	5	31	3	CVD_FEM_CTRL	40	68	12	28	12
8060	A G	HELD_FEM_LOHDL	18	29	7	11	7	HELD_FEM_HIHDL	23	43	3	20	3
8210	A G	HELD_FEM_HIRES	12	9	15	1	7	HELD_FEM_LORESP	22	22	22	9	4
8592	C T	HELD_FEM_VHIRESP	150	122	178	15	92	HELD_FEM_VLORESP	143	118	168	25	68
8816	C G	HELD_FEM_HIRES	13	15	11	4	7	HELD_FEM_LORESP	11	5	17	0	5
8846	A G	HELD_ALL_BAD	107	161	53	57	47	HELD_ALL_GOOD	116	166	66	62	42
8943	A C	HELD_MAL_BAD	20	35	5	15	5	HELD_MAL_GOOD	37	52	22	20	12
9193	C G	HELD_FEM_BAD	83	155	11	72	11	HELD_FEM_GOOD	80	140	20	60	20
9193	C G	CVD_FEM_CASE	36	63	9	28	7	CVD_FEM_CTRL	40	77	3	37	3
9443	C T	CVD_MAL_CASE	69	43	95	9	25	CVD_MAL_CTRL	33	12	54	0	12
9516	A G	HELD_MAL_CASE	14	17	11	7	3	HELD_MAL_CTRL	18	12	24	2	8
9698	A G	HELD_MAL_ADRCASE	74	8	140	4	0	HELD_MAL_ADRCTRL	72	30	114	14	2
9698	A G	HELD_MAL_ADRCASE3ULN	27	54	0	0	0	HELD_MAL_ADRCTRL	72	30	114	14	2
9698	A G	HELD_FEM_HIRES	294	105	483	5	95	HELD_FEM_LORESP	298	123	473	16	91
9698	A G	HELD_MAL_ADRCASE5ULN	10	20	0	0	0	HELD_MAL_ADRCTRL	72	30	114	14	2

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SNP	Alt	COHORT A	SIZE A	FO1A	FO2A	FO1A	FO2A	FO1A	FO2A	COHORT B	SIZE B	FO1B	FO2B	FO1B	FO2B
9698	A G	CVD_ALL_CASE	102	46	158	17	12	73	72	CVD_ALL_CTRL	72	19	125	6	59
9849	C T	HELD_FEM_CASE	31	62	0	31	0	0	21	HELD_FEM_CTRL	21	39	3	18	0
9849	C T	HELD_MAL_BAD	20	35	5	15	5	0	37	HELD_MAL_GOOD	37	72	2	35	0
9883	A G	HELD_FEM_CASE	31	23	39	7	9	15	22	HELD_FEM_CTRL	22	18	26	1	5
9883	A G	HELD_ALL_CASE	45	33	57	9	15	21	39	HELD_ALL_CTRL	39	32	46	4	11
10079	A G	CVD_ALL_CASE	103	8	198	4	0	99	73	CVD_ALL_CTRL	73	1	145	0	72
10079	A G	CVD_MAL_CASE	68	8	128	4	0	64	34	CVD_MAL_CTRL	34	68	0	0	34
10481	A T	HELD_FEM_ADRCASE5ULN	17	12	22	3	6	8	83	HELD_FEM_ADRCTRL	83	97	69	32	18
10542	C T	HELD_FEM_UHIRESP	54	8	100	1	6	47	75	HELD_FEM_ULORESP	75	21	129	0	54
10542	C T	HELD_MAL_ADRCASE5ULN	10	20	0	0	0	10	69	HELD_MAL_ADRCTRL	69	14	124	0	55
10600	A G	HELD_FEM_HIRES	21	42	0	0	0	21	33	HELD_FEM_LORESP	33	4	62	0	29
10621	C T	HELD_FEM_CASE	30	52	8	24	4	2	20	HELD_FEM_CTRL	20	32	8	12	0
10745	A G	HELD_ALL_ADRCASE5ULN	27	20	34	5	10	12	148	HELD_ALL_ADRCTRL	148	75	221	7	80
10745	A G	HELD_FEM_VHIRESP	153	90	216	11	68	74	150	HELD_FEM_VLORESP	150	77	223	16	89
10747	C T	HELD_MAL_ADRCASE	76	74	78	14	46	16	70	HELD_MAL_ADRCTRL	70	64	76	3	9
10747	C T	CVD_ALL_CASE	62	54	70	15	24	23	74	CVD_ALL_CTRL	74	51	97	6	29
10747	C T	HELD_MAL_ADRCASE3ULN	27	24	30	4	16	7	70	HELD_MAL_ADRCTRL	70	64	76	3	9
10771	C G	HELD_MAL_ADRCASE5ULN	10	12	8	4	4	2	70	HELD_MAL_ADRCTRL	70	48	92	6	28
10771	C G	HELD_FEM_HIRES	284	222	346	52	118	114	276	HELD_FEM_LORESP	276	185	367	40	131
10870	A G	HELD_MAL_BAD	20	11	29	0	11	9	37	HELD_MAL_GOOD	37	19	55	5	23
10870	A G	HELD_FEM_BAD	82	32	132	7	18	57	77	HELD_FEM_GOOD	77	46	108	8	39
10870	A G	HELD_MAL_CASE	14	3	25	0	3	11	18	HELD_MAL_CTRL	18	12	24	2	8
10870	A G	HELD_ALL_CASE	45	17	73	2	13	30	40	HELD_ALL_CTRL	40	27	53	6	19
10877	A C	HELD_ALL_LOHDL	9	18	0	0	0	9	15	HELD_ALL_HIHDL	15	7	23	1	9
10948	G T	HELD_FEM_BAD	84	83	85	16	51	17	79	HELD_FEM_GOOD	79	95	63	31	15
10948	G T	HELD_ALL_BAD	104	104	104	22	60	22	115	HELD_ALL_GOOD	115	138	92	44	21

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DaysNP	At A2	COHORT A	SIZE A	FO1A	FO2A	FO1A	FO2A	FO1A	FO2A	COHORT B	SIZE B	FO1B	FO2B	FO1B	FO2B
10948	G T	HELD_FEM_CASE2	44	46	42	9	28	7	HELD_FEM_CTRL2	42	50	34	17	16	9
10948	G T	CVD_MAL_CASE	69	63	75	12	39	18	CVD_MAL_CTRL	34	41	27	12	17	5
11001	C T	HELD_MAL_ADRCASE5UJLN	10	9	11	2	5	3	HELD_MAL_ADRCTRL	75	41	109	2	37	36
11073	C G	HELD_MAL_ADRCASE5UJLN	9	10	8	3	4	2	HELD_MAL_ADRCTRL	68	43	93	9	25	34
11153	C T	HELD_FEM_CASE	31	55	7	24	7	0	HELD_FEM_CTRL	22	33	11	11	11	0
11210	C T	HELD_MAL_CASE	14	23	5	9	5	0	HELD_MAL_CTRL	19	37	1	18	1	0
11210	C T	HELD_ALL_ADRCASE3UJLN	63	110	16	47	16	0	HELD_ALL_ADRCTRL	144	267	21	125	17	2
11210	C T	HELD_ALL_ADRCASE	153	275	31	122	31	0	HELD_ALL_ADRCTRL	144	267	21	125	17	2
11248	C T	HELD_FEM_ADRCASE	81	131	31	56	19	6	HELD_FEM_ADRCTRL	79	112	46	38	36	5
11248	C T	HELD_MAL_BAD	18	33	3	15	3	0	HELD_MAL_GOOD	34	53	15	19	15	0
11248	C T	HELD_ALL_CASE	41	68	14	27	14	0	HELD_ALL_CTRL	31	44	18	13	18	0
11372	A G	HELD_MAL_BAD	20	25	15	10	5	5	HELD_MAL_GOOD	36	31	41	10	11	15
11449	C G	HELD_FEM_CASE	31	6	56	1	4	26	HELD_FEM_CTRL	22	10	34	0	10	12
11450	A T	HELD_FEM_HIRES	289	170	408	28	114	147	HELD_FEM_LORESP	290	139	441	16	107	167
11470	C T	HELD_MAL_BAD	20	40	0	20	0	0	HELD_MAL_GOOD	36	67	5	31	5	0
11472	A T	HELD_MAL_BAD	20	40	0	20	0	0	HELD_MAL_GOOD	35	65	5	30	5	0
11472	A T	HELD_FEM_BAD	83	158	8	75	8	0	HELD_FEM_GOOD	80	158	2	78	2	0
11487	A T	HELD_MAL_ADRCASE5UJLN	10	20	0	0	10	0	HELD_MAL_ADRCTRL	69	34	104	34	35	0
11487	A T	HELD_MAL_ADRCASE3UJLN	27	6	48	6	21	0	HELD_MAL_ADRCTRL	69	34	104	34	35	0
11488	C G	HELD_MAL_ADRCASE5UJLN	10	20	0	10	0	0	HELD_MAL_ADRCTRL	70	102	38	35	32	3
11488	C G	HELD_FEM_UHIRESP	54	78	30	29	20	5	HELD_FEM_ULORESP	77	126	28	49	28	0
11488	C G	HELD_MAL_ADRCASE3UJLN	26	44	8	20	4	2	HELD_MAL_ADRCTRL	70	102	38	35	32	3
11493	A G	HELD_MAL_CASE	14	6	22	0	6	8	HELD_MAL_CTRL	18	6	30	2	2	14
11502	C T	HELD_MAL_ADRCASE3UJLN	27	8	46	0	8	19	HELD_MAL_ADRCTRL	73	44	102	7	30	36
11502	C T	HELD_MAL_ADRCASE5UJLN	10	2	18	0	2	8	HELD_MAL_ADRCTRL	73	44	102	7	30	36
11534	G T	HELD_ALL_BAD	102	204	0	102	0	0	HELD_ALL_GOOD	117	231	3	114	3	0

baySNP	AI/A2	COHORT A	SIZE	FQPA	FQPA	FQ1A	FQ1A	FQ1A	FQ1A	COHORT B	SIZE	FQ1B	FQ2B	FQ1B	FQ2B	FQ1B	FQ2B
			A			A	A	A	A		B	B	B	B	B	B	B
11537	A G	CVD_FEM_CASE	36	52	20	20	12	4		CVD_FEM_CTRL	39	68	10	30	8	1	
11537	A G	HELD_FEM_HIRES	12	22	2	10	2	0		HELD_FEM_LORESP	22	31	13	12	7	3	
11560	A G	HELD_FEM_HIRES	12	2	22	1	0	11		HELD_FEM_LORESP	22	44	0	0	0	22	
11578	C T	HELD_FEM_BAD	61	121	1	60	1	0		HELD_FEM_GOOD	65	122	8	57	8	0	
11578	C T	CVD_FEM_CASE	30	57	3	27	3	0		CVD_FEM_CTRL	39	78	0	39	0	0	
11594	C T	HELD_FEM_ADRCASE3ULN	37	74	0	0	0	37		HELD_FEM_ADRCTRL	80	10	150	2	6	72	
11594	C T	HELD_ALL_ADRCASESULN	27	54	0	0	0	27		HELD_ALL_ADRCTRL	151	20	282	2	16	133	
11594	C T	HELD_ALL_CASE	45	10	80	0	10	35		HELD_ALL_CTRL	41	3	79	0	3	38	
11594	C T	HELD_ALL_ADRCASE	155	9	301	1	7	147		HELD_ALL_ADRCTRL	151	20	282	2	16	133	
11594	C T	HELD_FEM_ADRCASESULN	18	36	0	0	0	18		HELD_FEM_ADRCTRL	80	10	150	2	6	72	
11624	C T	HELD_ALL_CASE	42	57	27	21	15	6		HELD_ALL_CTRL	40	60	20	20	20	0	
11624	C T	HELD_MAL_CASE	13	18	8	8	2	3		HELD_MAL_CTRL	18	27	9	9	9	0	
11624	C T	HELD_FEM_HIRES	12	22	2	10	2	0		HELD_FEM_LORESP	21	30	12	12	6	3	
11627	C T	HELD_ALL_CASE	45	58	32	20	18	7		HELD_ALL_CTRL	40	61	19	21	19	0	
11627	C T	HELD_MAL_CASE	14	18	10	7	4	3		HELD_MAL_CTRL	18	27	9	9	9	0	
11627	C T	HELD_FEM_HIRES	12	22	2	10	2	0		HELD_FEM_LORESP	22	31	13	12	7	3	
11644	A G	HELD_MAL_ADRCASESULN	10	2	18	0	2	8		HELD_MAL_ADRCTRL	68	40	96	7	26	35	
11650	A G	HELD_FEM_HIRES	291	157	425	26	105	160		HELD_FEM_LORESP	290	181	399	23	135	132	
11654	A G	HELD_ALL_ADRCASESULN	25	17	33	7	3	15		HELD_ALL_ADRCTRL	136	84	188	14	56	66	
11654	A G	HELD_FEM_ADRCASESULN	15	11	19	5	1	9		HELD_FEM_ADRCTRL	71	47	95	8	31	32	
11654	A G	HELD_FEM_ADRCASE3ULN	32	23	41	8	7	17		HELD_FEM_ADRCTRL	71	47	95	8	31	32	
11654	A G	HELD_ALL_ADRCASESULN	53	39	67	12	15	26		HELD_ALL_ADRCTRL	136	84	188	14	56	66	
11655	A C	HELD_ALL_ADRCASESULN	26	35	17	16	3	7		HELD_ALL_ADRCTRL	148	203	93	72	59	17	
11655	A C	HELD_FEM_ADRCASESULN	17	23	11	11	1	5		HELD_FEM_ADRCTRL	80	104	56	35	34	11	
11655	A C	HELD_FEM_ADRCASE3ULN	35	45	25	19	7	9		HELD_FEM_ADRCTRL	80	104	56	35	34	11	
11656	C T	HELD_MAL_BAD	20	20	20	6	8	6		HELD_MAL_GOOD	36	53	19	19	15	2	

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SNP	AT A2	COHORT A	SIZE A	FO1A	FO2A	FO1A	FO2A	FO1A	FO2A	COHORT B	SIZE B	FO1B	FO2B	FO1B	FO2B	FO1B	FO2B
11656	C T	HELD_FEM_HIRES	12	19	5	7	5	0	0	HELD_FEM_LORESP	22	24	20	5	14	3	3
11656	C T	HELD_ALL_BAD	102	119	85	35	49	18	18	HELD_ALL_GOOD	114	156	72	51	54	9	9
11825	A G	HELD_MAL_ADRCASESULN	9	15	3	6	3	0	0	HELD_MAL_ADRCTRL	63	121	5	58	5	0	0
11914	A T	HELD_MAL_ADRCASESULN	9	2	16	1	0	8	8	HELD_MAL_ADRCTRL	69	83	55	41	1	27	27
11914	A T	HELD_ALL_ADRCASESULN	27	24	30	6	12	9	9	HELD_ALL_ADRCTRL	151	178	124	63	52	36	36
12008	C T	HELD_FEM_HIRES	278	529	27	251	27	0	0	HELD_FEM_LORESP	277	541	13	264	13	0	0
12008	C T	HELD_ALL_ADRCASESULN	24	48	0	24	0	0	0	HELD_ALL_ADRCTRL	134	256	12	122	12	0	0
12097	A G	HELD_ALL_ADRCASESULN	28	6	50	6	22	0	0	HELD_ALL_ADRCTRL	155	11	299	11	144	0	0
12097	A G	HELD_FEM_ADRCASESULN	38	7	69	7	31	0	0	HELD_FEM_ADRCTRL	83	5	161	5	78	0	0
12097	A G	HELD_MAL_ADRCASESULN	10	3	17	3	7	0	0	HELD_MAL_ADRCTRL	72	6	138	6	66	0	0
12097	A G	HELD_ALL_ADRCASESULN	63	10	116	10	53	0	0	HELD_ALL_ADRCTRL	155	11	299	11	144	0	0
12366	A G	HELD_FEM_UHIRES	50	82	18	32	18	0	0	HELD_FEM_ULORESP	74	104	44	39	26	9	9
12366	A G	HELD_ALL_ADRCASESULN	25	40	10	18	4	3	3	HELD_ALL_ADRCTRL	151	229	73	85	59	7	7
12619	A G	HELD_MAL_ADRCASESULN	10	1	19	1	9	0	0	HELD_MAL_ADRCTRL	71	142	0	0	71	0	0
12619	A G	HELD_ALL_ADRCASESULN	27	2	52	2	25	0	0	HELD_ALL_ADRCTRL	151	1	301	1	150	0	0
13025	A C	HELD_ALL_ADRCASESULN	28	34	22	13	8	7	7	HELD_ALL_ADRCTRL	151	201	101	65	71	15	15
13191	A G	HELD_FEM_BAD	83	42	124	6	30	47	47	HELD_FEM_GOOD	79	62	96	10	42	27	27
13191	A G	HELD_MAL_CASE	14	11	17	2	7	5	5	HELD_MAL_CTRL	18	5	31	0	5	13	13
13191	A G	HELD_ALL_BAD	101	51	151	6	39	56	56	HELD_ALL_GOOD	114	81	147	13	55	46	46
13937	A C	HELD_FEM_ADRCASESULN	17	19	15	4	11	2	2	HELD_FEM_ADRCTRL	83	122	44	42	38	3	3
900002	G T	CVD_FEM_CASE	34	23	45	5	13	16	16	CVD_FEM_CTRL	40	15	65	2	11	27	27
900013	C G	CVD_FEM_CASE	35	49	21	20	9	6	6	CVD_FEM_CTRL	40	49	31	13	23	4	4
900013	C G	CVD_ALL_CASE	104	150	58	58	34	12	12	CVD_ALL_CTRL	74	97	51	29	39	6	6
900025	G T	CVD_MAL_CASE	66	41	91	7	27	32	32	CVD_MAL_CTRL	34	31	37	7	17	10	10
900032	C T	CVD_FEM_CASE	25	47	3	23	1	1	1	CVD_FEM_CTRL	37	65	9	28	9	0	0
900045	C T	HELD_FEM_HIRES	12	4	20	1	2	9	9	HELD_FEM_LORESP	22	18	26	5	8	9	9

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STSNP	AD12	COHORT A	SIZE A	FO1A	FO2A	FO1H	FO12	FO22	COHORT B	SIZE B	FO1B	FO2B	FO1H	FO12	FO22
900065	A C	CVD_FEM_CASE	32	54	10	22	10	0	CVD_FEM_CTRL	39	50	28	16	18	5
900065	A C	CVD_MAL_CASE	59	80	38	25	30	4	CVD_MAL_CTRL	29	36	22	7	22	0
900065	A C	CVD_ALL_CASE	91	134	48	47	40	4	CVD_ALL_CTRL	68	86	50	23	40	5
900078	A G	HELD_ALL_ADRCASE3ULN	64	116	12	52	12	0	HELD_ALL_ADRCTRL	155	297	13	142	13	0
900078	A G	HELD_ALL_ADRCASE5ULN	27	48	6	21	6	0	HELD_ALL_ADRCTRL	155	297	13	142	13	0
900078	A G	HELD_FEM_ADRCASE3ULN	38	69	7	31	7	0	HELD_FEM_ADRCTRL	83	161	5	78	5	0
900082	A G	HELD_FEM_ADRCASE3ULN	35	25	45	8	9	18	HELD_FEM_ADRCTRL	74	70	78	17	36	21
900082	A G	HELD_FEM_ADRCASE5ULN	17	10	24	3	4	10	HELD_FEM_ADRCTRL	74	70	78	17	36	21
900096	A G	CVD_ALL_CASE	101	157	45	60	37	4	CVD_ALL_CTRL	72	125	19	55	15	2
900107	C T	HELD_MAL_ADRCASE5ULN	10	2	18	0	2	8	HELD_MAL_ADRCTRL	73	43	103	9	25	39
900115	A G	HELD_MAL_ADRCASE5ULN	9	6	12	1	4	4	HELD_MAL_ADRCTRL	72	91	53	27	37	8
900115	A G	HELD_FEM_HIRES	40	58	22	22	14	4	HELD_FEM_LORESP	46	62	30	17	28	1
900121	G T	HELD_MAL_ADRCASE	66	47	85	5	37	24	HELD_MAL_ADRCTRL	67	56	78	15	26	26
900173	G T	CVD_ALL_CASE	23	17	29	5	7	11	CVD_ALL_CTRL	22	26	18	11	4	7
10000002	A G	HELD_FEM_HIRES	12	21	3	9	3	0	HELD_FEM_LORESP	22	25	19	9	7	6
10000006	A G	HELD_FEM_CASE	31	58	4	28	2	1	HELD_FEM_CTRL	22	31	13	11	9	2
10000006	A G	HELD_ALL_CASE	44	82	6	39	4	1	HELD_ALL_CTRL	38	58	18	23	12	3
10000014	A C	HELD_ALL_CASE	45	83	7	40	3	2	HELD_ALL_CTRL	39	64	14	26	12	1
10000014	A C	HELD_FEM_CASE	31	58	4	28	2	1	HELD_FEM_CTRL	22	37	7	15	7	0
10000025	C T	HELD_MAL_BAD	20	29	11	9	11	0	HELD_MAL_GOOD	36	43	29	14	15	7

Table 5b p-values of PA SNPs

A SNP is considered as associated to cardiovascular disease, adverse statin response or to efficacy of statin treatment, respectively, when one of the p values is equal or below 0.05.

BAVSNP	COMPARISON	GIYPE CPVAL	GIYPE XPVAL	GIYPE LRVAL	ADBBE CPVAL	ADBBE XPVAL	ADBBE LRVAL
28	HELD_FEM_EFF	0,0506	0,0508	0,0442	0,0411	0,0579	0,0349
29	HELD_ALL_HDL	0,021	0,0227	0,0099	0,0089	0,0164	0,0087
29	HELD_MAL_ADR3ULN	0,0602	0,0582	0,0664	0,0446	0,0526	0,0435
29	HELD_MAL_ADR5ULN	0,1406	0,1835	0,1554	0,0455	0,0778	0,0422
52	HELD_FEM_EFF	0,0644	0,0861	0,0488	0,0272	0,0362	0,0261
56	HELD_FEM_EFF	0,0248	0,0379	0,0273	0,0347	0,0479	0,0393
89	HELD_ALL_CC	0,0614	0,1	0,0311	0,0638	0,1021	0,0323
90	HELD_FEM_CC	0,0398	0,0424	0,0242	0,1382	0,1687	0,137
99	HELD_FEM_LIP	0,0363	0,0366	0,0338	0,8397	0,9056	0,8397
140	HELD_FEM_EFF	0,3895	0,6921	0,2368	0,1188	0,288	0,0524
152	HELD_FEM_EFF	0,1084	0,1216	0,1082	0,0373	0,0595	0,0389
214	HELD_ALL_LIP	0,1139	0,1152	0,0532	0,9756	1	0,9756
214	HELD_FEM_LIP	0,1095	0,1196	0,0506	0,5567	0,5803	0,5567
221	HELD_ALL_CC	0,0367	0,0359	0,0353	0,4257	0,506	0,426
221	HELD_FEM_CC	0,0406	0,0424	0,0384	0,1456	0,2083	0,1469
224	HELD_FEM_LIP	0,2893	0,3016	0,2874	0,0533	0,0709	0,0527
224	HELD_MAL_LIP	0,2292	0,2815	0,1975	0,0278	0,0392	0,0221
294	HELD_ALL_CC	0,0851	0,1041	0,0327	0,1547	0,1913	0,1534
307	CVD_FEM	0,013	0,0118	0,0104	0,0032	0,004	0,003
307	HELD_ALL_LIP	0,0255	0,0273	0,0249	0,0934	0,0968	0,0936

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BAVSNP	COMPARISON	GTTYPE CPVAL	GTTYPE XPVAL	GTTYPE LRPVAL	ALLELE CPVAL	ALLELE XPVAL	ALLELE LRPVAL
411	HELD_ALL_HDL	0,1529	0,2195	0,1076	0,0588	0,1136	0,0513
449	HELD_MAL_LIP	0,1321	0,0942	0,1001	0,0535	0,0667	0,0416
466	CVD_FEM	0,133	0,1439	0,1301	0,0444	0,0505	0,0438
472	HELD_FEM_EFF	0,0453	0,0626	0,0116	0,0068	0,0146	0,0009
542	HELD_MAL_CC	0,0014	0,0009	0,0007	0,0002	0,0003	0,0002
542	HELD_MAL_HDL	0,0054	0,0028	0,0029	0,0004	0,0005	0,0003
542	HELD_ALL_ADR	0,0257	0,0152	0,0171	0,0971	0,1108	0,0962
542	HELD_FEM_HDL	0,1914	0,1661	0,1457	0,0613	0,0709	0,0487
739	HELD_ALL_CC	0,0958	0,0983	0,0902	0,03	0,0327	0,0296
821	HELD_MAL_LIP2	0,0426	0,0436	0,0419	0,0865	0,0927	0,0867
821	HELD_FEM_VEFF	0,1193	0,1222	0,0584	0,0343	0,0681	0,0306
1005	HELD_MAL_CC	0,2376	0,3423	0,1618	0,0603	0,0946	0,0502
1055	HELD_MAL_CC	0,0302	0,0328	0,0084	0,2241	0,2988	0,216
1056	HELD_FEM_EFF	0,0094	0,0085	0,0079	0,9671	1	0,9671
1085	HELD_MAL_LIP	0,0889	0,0964	0,0773	0,0288	0,0462	0,0288
1085	CVD_FEM	0,1655	0,1833	0,156	0,0373	0,0546	0,0359
1086	HELD_MAL_LIP	0,0963	0,1125	0,0928	0,0318	0,0475	0,0315
1092	HELD_MAL_LIP	0,0493	0,0492	0,046	0,0712	0,0958	0,0663
1096	HELD_MAL_CC	0,0436	0,0623	0,0423	0,0685	0,0895	0,0679
1096	CVD_MAL	0,0766	0,0645	0,0452	0,5906	0,6848	0,5936
1101	HELD_FEM_EFF	0,1158	0,2728	0,0522	0,1279	0,2891	0,0572
1204	HELD_MAL_LIP	0,0471	0,0447	0,0362	0,0189	0,0238	0,0214
1204	HELD_ALL_LIP	0,1563	0,1592	0,1558	0,0422	0,0485	0,0424
1504	HELD_ALL_CC	0,0128	0,0133	0,0115	0,5946	0,64	0,5946
1504	HELD_MAL_LIP	0,0864	0,087	0,0247	0,1834	0,2241	0,1799

BAVENP	COMPARISON	CMPE CPVAL	CMPE MPVAL	CMPE URVAL	ABBLE CPVAL	ABBLE MPVAL	ABBLE URVAL
1504	HELD_MAL_CC	0,051	0,0757	0,0467	0,2868	0,3134	0,2871
1504	HELD_FEM_CC	0,0535	0,0663	0,0532	0,0878	0,1084	0,0873
1511	HELD_FEM_EFF	0,0513	0,0299	0,0413	0,1279	0,1563	0,1329
1524	HELD_FEM_ADR3ULN	0,0684	0,0673	0,0215	0,64	0,7419	0,6382
1556	HELD_FEM_EFF	0,0063	0,0151	0,0066	0,0129	0,0269	0,015
1561	CVD_FEM	0,1299	0,1484	0,1216	0,0472	0,0666	0,0456
1582	HELD_MAL_LIP	0,1444	0,1408	0,0649	0,0389	0,0633	0,0319
1638	HELD_FEM_CC	0,0876	0,0903	0,0861	0,0318	0,0385	0,0328
1653	CVD_MAL	0,0269	0,0234	0,0255	0,4812	0,5499	0,4809
1662	HELD_MAL_CC	0,0153	0,0278	0,0067	0,0006	0,0007	0,0001
1714	CVD_MAL	0,0716	0,0776	0,0817	0,0388	0,0484	0,041
1722	HELD_FEM_ADR5ULN	0,0325	0,0304	0,0429	0,1144	0,1401	0,1146
1757	HELD_FEM_EFF	0,0289	0,0296	0,0153	0,1752	0,1926	0,1779
1765	HELD_ALL_ADR3ULN	0,0044	0,0049	0,0024	0,0023	0,0029	0,0012
1765	HELD_ALL_ADR3ULN	0,0044	0,0049	0,0024	0,0023	0,0029	0,0012
1765	HELD_ALL_ADR5ULN	0,0469	0,0457	0,0235	0,0166	0,0163	0,0077
1765	HELD_ALL_ADR5ULN	0,0469	0,0457	0,0235	0,0166	0,0163	0,0077
1765	HELD_MAL_ADR3ULN	0,0428	0,0505	0,0211	0,0131	0,0174	0,0058
1765	HELD_MAL_ADR3ULN	0,0428	0,0505	0,0211	0,0131	0,0174	0,0058
1765	HELD_MAL_ADR5ULN	0,0997	0,0786	0,0255	0,0396	0,0451	0,0069
1765	HELD_MAL_ADR5ULN	0,0997	0,0786	0,0255	0,0396	0,0451	0,0069
1765	HELD_FEM_ADR3ULN	0,0666	0,0733	0,0522	0,0513	0,0579	0,0423
1765	HELD_FEM_ADR3ULN	0,0666	0,0733	0,0522	0,0513	0,0579	0,0423
1776	HELD_ALL_CC	0,0614	0,1	0,0311	0,0082	0,0098	0,0023
1776	HELD_FEM_CC	0,087	0,1676	0,0568	0,0155	0,0273	0,0071

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WAYSNP	COMPARISON	GRVPE CPVAL	GRVPE XPVAL	GRVPE IRVAL	ADDEE CPVAL	ADDEE XPVAL	ADDEE IRVAL
1799	HELD_FEM_LIP2	0,006	0,0058	0,0061	0,2598	0,268	0,2601
1799	HELD_MAL_CC	0,1419	0,1545	0,134	0,0408	0,0604	0,0406
1806	HELD_FEM_EFF	0,1946	0,236	0,128	0,047	0,0817	0,0299
1837	HELD_FEM_LIP2	0,0049	0,0047	0,0048	0,569	0,5843	0,5688
1837	HELD_ALL_LIP2	0,0085	0,0085	0,0084	0,0433	0,0445	0,0431
1837	HELD_ALL_ADRSULN	0,0159	0,015	0,0135	0,0245	0,0271	0,019
1837	HELD_MAL_ADR	0,0544	0,0558	0,0529	0,078	0,0897	0,0779
1837	HELD_MAL_LIP2	0,0694	0,0696	0,0684	0,0215	0,0237	0,0213
1870	HELD_ALL_CC	0,0213	0,018	0,0195	0,0874	0,1157	0,0854
1870	HELD_FEM_CC	0,0621	0,0435	0,059	0,0937	0,1293	0,0894
1882	CVD_MAL	0,0296	0,028	0,0055	0,4108	0,4529	0,4093
1988	HELD_ALL_LIP	0,1287	0,1307	0,1234	0,0385	0,0414	0,0379
2000	CVD_MAL	0,0237	0,0363	0,0295	0,0014	0,0025	0,0021
2000	CVD_ALL	0,034	0,0425	0,035	0,0027	0,0035	0,0029
2000	HELD_FEM_CC2	0,0705	0,0992	0,061	0,0105	0,0145	0,0081
2000	HELD_MAL_HDL	0,1671	0,489	0,1018	0,0507	0,1177	0,0207
2000	HELD_FEM_ADR	0,1624	0,2773	0,1528	0,0482	0,0704	0,0432
2000	HELD_MAL_CC	0,1597	0,2882	0,1581	0,0467	0,063	0,0459
2071	CVD_ALL	0,0823	0,09	0,0741	0,0349	0,0411	0,0339
2078	HELD_MAL_LIP	0,0667	0,0395	0,0572	0,0468	0,0583	0,0507
2085	HELD_FEM_VEFF	0,0707	0,0839	0,0347	0,019	0,0349	0,0165
2095	CVD_ALL	0,0917	0,1451	0,0384	0,0935	0,1473	0,0392
2119	HELD_MAL_LIP	0,0309	0,0409	0,0248	0,1269	0,148	0,1297
2119	HELD_ALL_LIP	0,0382	0,0476	0,0373	0,133	0,1514	0,1332
2119	HELD_FEM_EFF	0,057	0,0796	0,0527	0,1279	0,1563	0,1329

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BAVSNP	COMPARISON	GRUPE GRVAL	GRUPE XVAL	GRUPE LRVAL	ALTELE GRVAL	ALTELE XVAL	ALTELE LRVAL
2141	HELD_FEM_EFF	0,021	0,0256	0,0169	0,2401	0,3207	0,2483
2141	HELD_ALL_CC	0,079	0,0695	0,0439	0,9551	1	0,9551
2182	HELD_FEM_EFF	0,0038	0,0027	0,0014	0,0039	0,0051	0,0033
2234	HELD_MAL_LIP	0,0604	0,0581	0,0195	0,0315	0,0414	0,0289
2281	HELD_FEM_VEFF	0,1098	0,1234	0,0542	0,0501	0,0685	0,0472
2298	CVD_FEM	0,0241	0,0171	0,0108	0,9341	1	0,934
2298	HELD_MAL_CC2	0,1235	0,1076	0,0833	0,053	0,0671	0,0514
2341	HELD_FEM_CC	0,0284	0,0709	0,0083	0,0336	0,0796	0,0097
2357	HELD_ALL_CC2	0,042	0,0374	0,016	0,7724	0,8793	0,7723
2357	HELD_ALL_CC	0,0452	0,0325	0,0209	0,9622	1	0,9622
2357	HELD_MAL_LIP	0,0438	0,0824	0,0385	0,077	0,1278	0,0657
2357	HELD_FEM_CC	0,0772	0,0829	0,0381	0,6486	0,7985	0,6469
2366	CVD_FEM	0,1125	0,1171	0,1073	0,0234	0,0304	0,023
2423	CVD_FEM	0,086	0,0888	0,077	0,0185	0,0274	0,0179
2708	CVD_FEM	0,0719	0,1262	0,054	0,0813	0,1384	0,0609
2995	HELD_FEM_ADRSULN	0,0882	0,0827	0,1088	0,0448	0,0488	0,0503
2995	HELD_FEM_UEFF	0,0943	0,0942	0,0928	0,0516	0,0693	0,0495
3360	HELD_MAL_ADRSULN	0,1131	0,1691	0,0302	0,0499	0,0819	0,0097
3464	HELD_ALL_CC	0,0305	0,0331	0,0278	0,0047	0,0056	0,0046
3464	HELD_FEM_CC	0,0743	0,0777	0,0721	0,0141	0,0184	0,0144
3689	HELD_FEM_EFF	0,0488	0,0584	0,0295	0,0226	0,0378	0,0206
3975	HELD_FEM_UEFF	0,0492	0,0474	0,0407	0,0198	0,0237	0,0188
3976	HELD_FEM_UEFF	0,059	0,0605	0,0456	0,0262	0,0327	0,025
4206	HELD_FEM_ADRSULN	0,1395	0,1496	0,1372	0,0522	0,0655	0,0529
4838	HELD_FEM_VEFF	0,0581	0,0772	0,0529	0,0343	0,0681	0,0306

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DAVSNP	COMPARISON	GTYPF CPVAL	GTYPF XPVAL	GTYPF LRPVAL	ADDEE CPVAL	ADDEE XPVAL	ADDEE LRPVAL
4838	HELD_FEM_VEFF	0,0581	0,0772	0,0529	0,0343	0,0681	0,0306
4838	HELD_FEM_VEFF	0,0581	0,0772	0,0529	0,0343	0,0681	0,0306
4912	HELD_FEM_EFF	0,1257	0,1748	0,0921	0,0255	0,0361	0,0255
4925	HELD_MAL_CC	0,0436	0,0623	0,0423	0,0685	0,0895	0,0679
4966	HELD_MAL_ADR3ULN	0,0269	0,0282	0,0298	0,1675	0,1966	0,1669
5014	HELD_ALL_ADR3ULN	0,007	0,0104	0,0022	0,0738	0,0869	0,0611
5014	HELD_FEM_ADR3ULN	0,0574	0,0604	0,0276	0,2347	0,2691	0,2164
5296	CVD_FEM	0,0459	0,0738	0,0438	0,0585	0,0899	0,0558
5296	HELD_FEM_EFF	0,0703	0,0489	0,0461	0,4109	0,5177	0,4006
5296	CVD_ALL	0,145	0,1027	0,1148	0,0579	0,0771	0,0523
5298	HELD_FEM_EFF	0,0813	0,0465	0,0567	0,4984	0,7366	0,49
5298	CVD_ALL	0,107	0,1065	0,0603	0,0348	0,0376	0,0306
5298	CVD_FEM	0,1629	0,1593	0,1332	0,0511	0,0885	0,049
5320	HELD_FEM_EFF	0,037	0,0397	0,029	0,016	0,0243	0,0151
5361	CVD_MAL	0,0947	0,1065	0,0447	0,0519	0,0654	0,0518
5457	HELD_FEM_EFF	0,1213	0,134	0,0452	0,2429	0,3056	0,2246
5704	HELD_MAL_LIP	0,0385	0,0334	0,0406	0,054	0,0678	0,0503
5704	CVD_MAL	0,0701	0,0755	0,07	0,0246	0,0281	0,0259
5717	HELD_FEM_ADR3ULN	0,0736	0,0775	0,0739	0,0219	0,026	0,021
5717	HELD_ALL_ADR3ULN	0,1246	0,1264	0,1214	0,0391	0,0471	0,0389
5959	HELD_ALL_CC	0,0126	0,0122	0,0098	0,0046	0,0073	0,0044
5959	CVD_FEM	0,019	0,0225	0,0082	0,0089	0,0137	0,0083
5959	HELD_MAL_CC	0,0525	0,0589	0,0243	0,0536	0,0708	0,053
5959	HELD_MAL_ADR3ULN	0,038	0,0364	0,0482	0,1839	0,2158	0,1795
5959	HELD_FEM_ADR	0,054	0,0574	0,0527	0,0465	0,0539	0,0461

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PAUSEUP	COMPARISON	CTYPE CPVAL	CTYPE CPVAL	CTYPE CPVAL	CTYPE CPVAL	CTYPE CPVAL	CTYPE CPVAL	CTYPE CPVAL	CTYPE CPVAL
6162	HELD_ALL_ADR3ULN	0,0037	0,0034	0,0015	0,8524	0,9082	0,8522		
6162	HELD_ALL_ADR	0,0033	0,003	0,0028	0,663	0,722	0,663		
6162	HELD_ALL_ADR5ULN	0,0206	0,0248	0,006	0,9797	1	0,9797		
6162	HELD_MAL_ADR3ULN	0,0412	0,0352	0,0108	0,4721	0,4836	0,468		
6162	HELD_FEM_ADR3ULN	0,0274	0,0257	0,0147	0,4282	0,5487	0,4335		
6162	HELD_MAL_ADR	0,0219	0,0217	0,0188	0,5399	0,6036	0,5399		
6236	HELD_ALL_ADR5ULN	0,0477	0,0396	0,0641	0,0131	0,016	0,0158		
6236	HELD_MAL_ADR3ULN	0,0787	0,0734	0,0762	0,0279	0,0376	0,0305		
6236	HELD_MAL_ADR5ULN	0,0932	0,0861	0,0924	0,0297	0,0375	0,0368		
6236	HELD_ALL_ADR3ULN	0,1516	0,1516	0,1604	0,0474	0,051	0,0497		
6482	HELD_MAL_HDL	0,0359	0,0402	0,0326	0,009	0,013	0,0087		
6482	HELD_ALL_LIP2	0,0383	0,0381	0,0383	0,0486	0,0506	0,0487		
6482	HELD_MAL_CC2	0,0613	0,0667	0,0572	0,0114	0,0142	0,0106		
6482	HELD_MAL_LIP2	0,0651	0,0662	0,065	0,0357	0,04	0,0358		
6498	CVD_FEM	0,145	0,1987	0,0811	0,0323	0,0389	0,0281		
6744	HELD_ALL_ADR5ULN	0,0659	0,07	0,0775	0,02	0,0273	0,0243		
7133	HELD_MAL_CC	0,0153	0,0278	0,0067	0,0006	0,0007	0,0001		
8021	CVD_FEM	0,039	0,0422	0,0304	0,8726	1	0,8726		
8060	CVD_FEM	0,044	0,0304	0,0304	0,1299	0,1961	0,1237		
8060	HELD_FEM_HDL	0,0558	0,0753	0,0549	0,0759	0,0965	0,0753		
8210	HELD_FEM_EFF	0,0336	0,0396	0,0276	0,3226	0,4454	0,3207		
8592	HELD_FEM_VEFF	0,0395	0,0432	0,0388	0,8842	0,9331	0,8842		
8816	HELD_FEM_EFF	0,0448	0,0448	0,0202	0,0144	0,0199	0,0128		
8846	HELD_ALL_LIP	0,0628	0,0654	0,0521	0,3798	0,3932	0,3794		

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FAVSNP	COMPARISON	CTYPE CPVAL	CTYPE XPVAL	CTYPE LRVAL	ADDELE CPVAL	ADDELE XPVAL	ADDELE LRVAL
8943	HELD_MAL_LIP	0,1444	0,1408	0,0649	0,0389	0,0633	0,0319
9193	HELD_FEM_LIP	0,0561	0,0723	0,0548	0,0707	0,0889	0,0691
9193	CVD_FEM	0,1616	0,1289	0,1306	0,0458	0,0687	0,0424
9443	CVD_MAL	0,0828	0,0869	0,0213	0,0507	0,0634	0,0455
9516	HELD_MAL_CC	0,0504	0,0583	0,046	0,029	0,043	0,0283
9698	HELD_MAL_ADR	0,0106	0,0048	0,0061	0,0001	0,0001	0,0001
9698	HELD_MAL_ADRSULN	0,0279	0,0274	0,0035	0,0003	0,0002	0
9698	HELD_FEM_EFF	0,0538	0,0557	0,0464	0,2251	0,2386	0,2249
9698	HELD_MAL_ADRSULN	0,2515	0,3809	0,097	0,0239	0,0263	0,0032
9698	CVD_ALL	0,2256	0,2237	0,2119	0,0274	0,0357	0,025
9849	HELD_FEM_CC	0,0302	0,0602	0,0168	0,0327	0,063	0,0182
9849	HELD_MAL_LIP	0,0315	0,0448	0,0358	0,0376	0,0505	0,043
9883	HELD_FEM_CC	0,006	0,0053	0,0046	0,6913	0,8398	0,6915
9883	HELD_ALL_CC	0,0345	0,035	0,0331	0,5629	0,6344	0,563
10079	CVD_ALL	0,118	0,0767	0,048	0,0611	0,0864	0,0418
10079	CVD_MAL	0,1491	0,2983	0,0682	0,0413	0,054	0,0099
10481	HELD_FEM_ADRSULN	0,0697	0,0667	0,0774	0,0136	0,0149	0,0135
10542	HELD_FEM_UEFF	0,0374	0,0214	0,0265	0,0981	0,1126	0,0911
10542	HELD_MAL_ADRSULN	0,1163	0,1946	0,0404	0,1357	0,2186	0,046
10600	HELD_FEM_EFF	0,0973	0,1483	0,0418	0,104	0,1554	0,0445
10621	HELD_FEM_CC	0,0622	0,0649	0,0451	0,373	0,4126	0,3769
10745	HELD_ALL_ADRSULN	0,0329	0,0356	0,0723	0,0754	0,0953	0,0832
10745	HELD_FEM_VEFF	0,0308	0,0308	0,0302	0,3022	0,3181	0,302
10747	HELD_MAL_ADR	0,006	0,0053	0,0044	0,6116	0,64	0,6115
10747	CVD_ALL	0,0285	0,0292	0,027	0,1252	0,1349	0,1253

WAYSIP	COMPARISON	GYTPE CPVAL	GYTPE XPVAL	GYTPE LRVAL	ALTEHE CPVAL	ALTEHE XPVAL	ALTEHE LRVAL
10747	HELD_MAL_ADR3ULN	0,0401	0,0412	0,0505	0,8735	1	0,8734
10771	HELD_MAL_ADR5ULN	0,0176	0,0191	0,0469	0,0263	0,0458	0,0291
10771	HELD_FEM_EFF	0,1837	0,1844	0,1832	0,0527	0,0543	0,0525
10870	HELD_MAL_LIP	0,0323	0,0272	0,0156	0,8328	1	0,8332
10870	HELD_FEM_LIP	0,0431	0,0412	0,0421	0,0319	0,037	0,0317
10870	HELD_MAL_CC	0,1157	0,0954	0,0779	0,0341	0,0413	0,0285
10870	HELD_ALL_CC	0,1146	0,1205	0,109	0,0272	0,0351	0,027
10877	HELD_ALL_HDL	0,0907	0,1181	0,0333	0,0266	0,0356	0,007
10948	HELD_FEM_LIP	0,0134	0,0136	0,0127	0,052	0,0588	0,0517
10948	HELD_ALL_LIP	0,0209	0,0207	0,0197	0,0356	0,0432	0,0355
10948	HELD_FEM_CC2	0,0513	0,0521	0,0493	0,3385	0,3602	0,3382
10948	CVD_MAL	0,0986	0,0986	0,103	0,0481	0,0548	0,0475
11001	HELD_MAL_ADR5ULN	0,0438	0,0618	0,1215	0,1034	0,1201	0,1152
11073	HELD_MAL_ADR3ULN	0,1741	0,1866	0,1892	0,0446	0,0632	0,0503
11153	HELD_FEM_CC	0,0378	0,0459	0,038	0,064	0,0726	0,0658
11210	HELD_MAL_CC	0,025	0,0616	0,0225	0,0335	0,0756	0,0304
11210	HELD_ALL_ADR3ULN	0,0344	0,027	0,0311	0,076	0,0917	0,0844
11210	HELD_ALL_ADR	0,0536	0,038	0,0354	0,2211	0,2468	0,2195
11248	HELD_FEM_ADR	0,0125	0,0119	0,0118	0,0368	0,0494	0,0364
11248	HELD_MAL_LIP	0,0478	0,0677	0,0404	0,0784	0,1038	0,0644
11248	HELD_ALL_CC	0,0431	0,0567	0,0425	0,0874	0,1066	0,0887
11372	HELD_MAL_LIP	0,2326	0,2665	0,2343	0,0486	0,0753	0,0477
11449	HELD_FEM_CC	0,0245	0,0119	0,0204	0,0644	0,0971	0,0663
11450	HELD_FEM_EFF	0,0922	0,0949	0,0903	0,0362	0,0394	0,036
11470	HELD_MAL_LIP	0,0807	0,1484	0,0304	0,0882	0,1582	0,033

FAVSNP	COMPARISON	GMPL GVAL	GMPL XVAL	GMPL LRVAL	AMBL GVAL	AMBL XVAL	AMBL LRVAL
11472	HELD_MAL_LIP	0,0763	0,1465	0,0284	0,0836	0,1565	0,031
11472	HELD_FEM_LIP	0,0576	0,0991	0,0495	0,0617	0,1046	0,053
11487	HELD_MAL_ADR3ULN	0,0033	0,0039	0,0004	0,0122	0,0159	0,0012
11487	HELD_MAL_ADR3ULN	0,0156	0,021	0,0131	0,038	0,0474	0,0295
11488	HELD_MAL_ADR3ULN	0,0117	0,0227	0,0018	0,0076	0,0087	0,0006
11488	HELD_FEM_UEFF	0,0217	0,021	0,0091	0,0655	0,0713	0,0672
11488	HELD_MAL_ADR3ULN	0,0239	0,0311	0,0166	0,0898	0,127	0,0797
11493	HELD_MAL_CC	0,0736	0,0542	0,0493	0,6283	0,7502	0,6293
11502	HELD_MAL_ADR3ULN	0,0881	0,0865	0,0363	0,0283	0,0301	0,0225
11502	HELD_MAL_ADR3ULN	0,1706	0,154	0,1118	0,0592	0,0659	0,0396
11534	HELD_ALL_LIP	0,1034	0,2501	0,0513	0,1046	0,2518	0,0519
11537	CVD_FEM	0,1061	0,1119	0,0989	0,0221	0,0256	0,0214
11537	HELD_FEM_EFF	0,1916	0,2436	0,1166	0,0438	0,0655	0,0324
11560	HELD_FEM_EFF	0,1693	0,3529	0,1436	0,0519	0,1212	0,0386
11578	HELD_FEM_LIP	0,0201	0,0333	0,0132	0,0226	0,0366	0,0147
11578	CVD_FEM	0,0435	0,0775	0,0229	0,0459	0,0799	0,0241
11594	HELD_FEM_ADR3ULN	0,1373	0,2125	0,0418	0,0279	0,0331	0,0052
11594	HELD_ALL_ADR3ULN	0,1669	0,1552	0,0434	0,0516	0,0536	0,0092
11594	HELD_ALL_CC	0,0539	0,0724	0,0479	0,0648	0,0846	0,0574
11594	HELD_ALL_ADR	0,1052	0,0878	0,1	0,0304	0,036	0,0286
11594	HELD_FEM_ADR3ULN	0,3753	0,4458	0,1824	0,1236	0,213	0,0409
11624	HELD_ALL_CC	0,0352	0,0383	0,0111	0,3119	0,388	0,3111
11624	HELD_MAL_CC	0,032	0,0313	0,0164	0,6153	0,7739	0,6163
11624	HELD_FEM_EFF	0,2292	0,244	0,1389	0,053	0,0656	0,0407
11627	HELD_ALL_CC	0,0337	0,0316	0,0088	0,0936	0,1309	0,0921

DAVSNP	COMPARISON	GTYP	GTYP CPVAL	GTYP XPVAL	GTYP LRVAL	ADDD CPVAL	ADDD XPVAL	ADDD LRVAL
I1627	HELD_MAL_CC	0,0931		0,0933	0,0528	0,352	0,4146	0,3531
I1627	HELD_FEM_EFF	0,1916		0,2436	0,1166	0,0438	0,0655	0,0324
I1644	HELD_MAL_ADR3ULN	0,2097		0,2525	0,1344	0,0676	0,1027	0,0467
I1650	HELD_FEM_EFF	0,0366		0,0361	0,0363	0,1123	0,1212	0,1122
I1654	HELD_ALL_ADR3ULN	0,0052		0,0046	0,0042	0,6623	0,7404	0,6642
I1654	HELD_FEM_ADR3ULN	0,0104		0,0096	0,006	0,7072	0,832	0,7087
I1654	HELD_FEM_ADR3ULN	0,0546		0,0592	0,0524	0,6906	0,7512	0,6913
I1654	HELD_ALL_ADR3ULN	0,052		0,0518	0,0601	0,2706	0,2742	0,2735
I1655	HELD_ALL_ADR3ULN	0,0085		0,0074	0,0058	0,8555	0,8723	0,8558
I1655	HELD_FEM_ADR3ULN	0,0136		0,0138	0,0053	0,7681	0,8443	0,7672
I1655	HELD_FEM_ADR3ULN	0,0489		0,048	0,0432	0,9169	1	0,9169
I1656	HELD_MAL_LIP	0,0321		0,0317	0,0346	0,012	0,0141	0,0126
I1656	HELD_FEM_EFF	0,0782		0,0909	0,0511	0,0442	0,0652	0,0393
I1656	HELD_ALL_LIP	0,0617		0,0646	0,06	0,0295	0,0353	0,0295
I1825	HELD_MAL_ADR3ULN	0,0233		0,056	0,0499	0,0278	0,0619	0,0612
I1914	HELD_MAL_ADR3ULN	0,0186		0,0915	0,0128	0,0001	0,0001	0
I1914	HELD_ALL_ADR3ULN	0,1572		0,1781	0,1391	0,0477	0,0533	0,0487
I2008	HELD_FEM_EFF	0,0222		0,0317	0,0209	0,0249	0,0351	0,0234
I2008	HELD_ALL_ADR3ULN	0,1272		0,2155	0,0422	0,135	0,225	0,0445
I2097	HELD_ALL_ADR3ULN	0,0162		0,0277	0,0308	0,019	0,0313	0,0367
I2097	HELD_FEM_ADR3ULN	0,0342		0,0487	0,042	0,0392	0,0543	0,0484
I2097	HELD_MAL_ADR3ULN	0,04		0,0749	0,0726	0,0462	0,081	0,0857
I2097	HELD_ALL_ADR3ULN	0,0465		0,073	0,056	0,0524	0,0805	0,0633
I2366	HELD_FEM_UEFF	0,0342		0,0313	0,0069	0,0364	0,0514	0,0338
I2366	HELD_ALL_ADR3ULN	0,0464		0,0391	0,0411	0,5197	0,5929	0,5131

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BAVSNP	COMPARISON	GRVPE GRVAL	GRVPE SRVAL	GRVPE LRVAL	ADBELE GRVAL	ADBELE SRVAL	ADBELE LRVAL
12619	HELD_MAL_ADRSULN	0,0073	0,1235	0,0387	0,0075	0,1235	0,0398
12619	HELD_ALL_ADRSULN	0,0121	0,0605	0,0414	0,0125	0,0613	0,0427
13025	HELD_ALL_ADRSULN	0,044	0,0399	0,0593	0,3978	0,4443	0,4018
13191	HELD_FEM_LIP	0,0157	0,0149	0,015	0,0072	0,0088	0,0071
13191	HELD_MAL_CC	0,0648	0,0601	0,0431	0,0199	0,0396	0,0196
13191	HELD_ALL_LIP	0,0634	0,0669	0,0616	0,0211	0,0217	0,0206
13937	HELD_FEM_ADRSULN	0,076	0,0835	0,0789	0,0402	0,0615	0,0462
900002	CVD_FEM	0,1492	0,1674	0,1456	0,0364	0,04	0,0364
900013	CVD_FEM	0,0212	0,022	0,0192	0,2613	0,3039	0,2602
900013	CVD_ALL	0,0279	0,0289	0,0279	0,1847	0,2004	0,1858
900025	CVD_MAL	0,1379	0,1533	0,1361	0,0426	0,0452	0,0439
900032	CVD_FEM	0,0555	0,036	0,0317	0,2549	0,3578	0,2418
900045	HELD_FEM_EFF	0,162	0,2388	0,151	0,0411	0,0579	0,0349
900065	CVD_FEM	0,0222	0,0175	0,0086	0,0066	0,0077	0,0057
900065	CVD_MAL	0,0549	0,0421	0,0289	0,4512	0,5001	0,453
900065	CVD_ALL	0,0773	0,0753	0,0754	0,0471	0,0505	0,0477
900078	HELD_ALL_ADR3ULN	0,0283	0,036	0,0348	0,0335	0,0417	0,0415
900078	HELD_ALL_ADR5ULN	0,03	0,0417	0,0487	0,0349	0,0466	0,0574
900078	HELD_FEM_ADR3ULN	0,0342	0,0487	0,042	0,0392	0,0543	0,0484
900082	HELD_FEM_ADR3ULN	0,0377	0,0378	0,0364	0,1073	0,111	0,1055
900082	HELD_FEM_ADR5ULN	0,0517	0,0587	0,0566	0,0581	0,0837	0,0542
900096	CVD_ALL	0,0644	0,0622	0,0602	0,032	0,0354	0,0294
900107	HELD_MAL_ADRSULN	0,2371	0,2767	0,1405	0,0665	0,1045	0,0455
900115	HELD_MAL_ADRSULN	0,0214	0,02	0,0409	0,0148	0,0208	0,0158
900115	HELD_FEM_EFF	0,0347	0,0338	0,0316	0,4668	0,5083	0,4661

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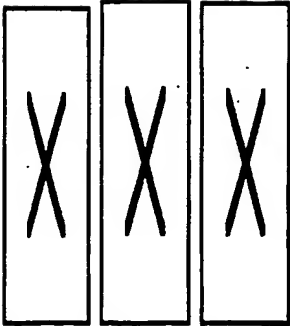
BAVSNP	COMPARISON	GMPL CPVAL	GMPL XPRVAL	GMPL IRPRVAL	AUDEL CPVAL	AUDEL XPRVAL	AUDEL IRPRVAL
900121	HELD_MAL_ADR	0,0303	0,0297	0,0268	0,3005	0,3162	0,3003
900173	CVD_ALL	0,1397	0,146	0,1347	0,0356	0,0569	0,0349
10000002	HELD_FEM_EFF	0,0781	0,0766	0,0305	0,0098	0,0139	0,0067
10000006	HELD_FEM_CC	0,0041	0,0018	0,0035	0,0014	0,0024	0,0014
10000006	HELD_ALL_CC	0,0127	0,0087	0,0113	0,0023	0,0034	0,002
10000014	HELD_ALL_CC	0,0156	0,0099	0,013	0,0468	0,0612	0,046
10000014	HELD_FEM_CC	0,0415	0,0248	0,0336	0,1157	0,1943	0,1184
10000025	HELD_MAL_LIP	0,1055	0,1309	0,0337	0,1763	0,2188	0,1719

Table 6a Correlation of genotypes of PA SNPs to relative risk

For diagnostic conclusions to be drawn from genotyping a particular patient we calculated the relative risk RR1, RR2, RR3 for the three possible genotypes of each SNP. Given the genotype frequencies as

	gtype1	gtype2	gtype3
case	N11	N12	N13
control	N21	N22	N23

we calculate



Here, the *case* and *control* populations represent any case-control-group pair, or bad(case)-good(control)-group pair, respectively (due to their increased response to statins, 'high responders' are treated as a case cohort, whereas 'low responders' are treated as the respective control cohort). A value $RR1 > 1$, $RR2 > 1$, and $RR3 > 1$ indicates an increased risk for individuals carrying genotype 1, genotype 2, and genotype 3, respectively. For example, $RR1 = 3$ indicates a 3-fold risk of an individual carrying genotype 1 as compared to individuals carrying genotype 2 or 3 (a detailed

description of relative risk calculation and statistics can be found in (Biostatistics, L. D. Fisher and G. van Belle, Wiley Interscience 1993)). The baySNP number refers to an internal numbering of the PA SNPs and can be found in the sequence listing. null: not defined.

In cases where a relative risk is not given in the table (three times zero or null) the informative genotype can be drawn from the right part of the table where the frequencies of genotypes are given in the cases and control cohorts. For example BaySNP 3360 gave the following results:

BAYSNP	COMPARISON	GTTYPE1	GTTYPE2	GTTYPE3	RR1	RR2	RR3
3360	HELD_MAL_ADR5ULN	GG	GT	TT	null	0	0

FQ1_A	FQ2_A	FQ3_A	FQ1_B	FQ2_B	FQ3_B
10	0	0	50	22	1

It can be concluded that a GT or TT genotype is only present in the control cohort; these genotypes are somehow protective against ADR. An analogous proceeding can be used to determine protective alleles if no relative risk is given (table 6b).

BAVSNP	COMPARISON	CI/YPE1	CI/YPE2	CI/YPE3	RR1	RR2	RR3	FO1A	FO2A	FO3A	FO1B	FO2B	FO3B
28	HELD_FEM_EFF	CC	CT	TT	0,68	0,29	3,38	1	2	9	3	12	7
29	HELD_ALL_HDL	AA	AG	GG	0	0,90	0,58	4	4	2	0	7	8
29	HELD_MAL_ADRSULN	AA	AG	GG	2,16	0,56	0,75	13	7	6	18	32	22
29	HELD_MAL_ADRSULN	AA	AG	GG	3,15	0,66	0,32	5	3	1	18	32	22
52	HELD_FEM_EFF	CC	CG	GG	1,96	1,02	0,23	7	10	1	5	17	9
56	HELD_FEM_EFF	AA	AG	GG	null	2,76	0,36	0	5	7	0	2	20
89	HELD_ALL_CC	AA	AG	null	null	0	null	45	0	0	37	3	0
90	HELD_FEM_CC	CC	CT	TT	0,97	0,64	1,82	8	13	10	6	15	1
99	HELD_FEM_LIP	CC	CT	TT	1,51	0,7	1,16	13	28	41	5	41	34
140	HELD_FEM_EFF	CC	CT	TT	0	0	null	0	0	12	1	2	18
152	HELD_FEM_EFF	AA	AG	GG	0,42	1,27	2,5	3	6	3	12	9	1
214	HELD_ALL_LIP	AA	AG	GG	0,92	1,18	0	59	38	0	73	36	4
214	HELD_FEM_LIP	AA	AG	GG	1	1,11	0	50	31	0	48	26	4
221	HELD_ALL_CC	CC	CG	GG	1,36	0,56	1,44	7	12	26	3	21	15
221	HELD_FEM_CC	CC	CG	GG	1,16	0,53	1,67	4	9	18	2	14	6
224	HELD_FEM_LIP	CC	CT	TT	0,77	1,26	1,24	51	8	20	60	5	14
224	HELD_MAL_LIP	CC	CT	TT	2,02	1,45	0,38	17	1	2	25	1	11
294	HELD_ALL_CC	CC	CT	TT	0,83	0,97	2	16	24	5	18	22	0
307	CVD_FEM	CC	CT	TT	0,34	0,8	1,84	2	15	19	9	20	9
307	HELD_ALL_LIP	CC	CT	TT	null	1,41	0,71	0	70	32	0	63	54
411	HELD_ALL_HDL	AA	AT	TT	1,85	0,69	0,56	7	3	0	5	8	2
449	HELD_MAL_LIP	CC	CG	GG	0	0,42	2,62	0	3	17	1	14	22
466	CVD_FEM	CC	CT	TT	0,66	0,86	1,61	6	15	14	12	20	8
472	HELD_FEM_EFF	AA	AG	GG	0	0	null	0	0	11	3	6	13
542	HELD_MAL_CC	AA	AG	GG	2,58	3,07	0,23	2	8	4	0	2	17

EWISNP	COMPARISON	GVPE1	GVPE2	GVPE3	RR1	RR2	RR3	FQ1A	FQ2A	FQ3A	FQ1B	FQ2B	FQ3B
542	HELD_MAL_HDL	AA	AG	GG	0	2,38	0,30	3	8	10	0	3	24
542	HELD_ALL_ADR	AA	AG	GG	0	1,32	0,78	0	53	106	2	33	119
542	HELD_FEM_HDL	AA	AG	GG	0,57	0,67	1,56	0	2	21	1	8	23
739	HELD_ALL_CC	CC	CG	GG	0,67	0,94	1,52	9	21	15	14	20	6
821	HELD_MAL_LIP2	AA	AC	CC	1,4	0,96	0,93	32	116	161	18	138	193
821	HELD_FEM_VEFF	AA	AC	CC	0	0,93	2,1	0	4	6	4	6	4
1005	HELD_MAL_CC	AA	AG	GG	2,35	0,6	0	12	2	0	11	5	2
1055	HELD_MAL_CC	AA	AT	TT	0	3	1	0	3	6	4	0	8
1056	HELD_FEM_EFF	AA	AG	GG	1,59	0,37	2,04	12	6	6	10	21	2
1085	HELD_MAL_LIP	AA	AG	GG	0,37	1,31	1,75	3	11	6	15	16	5
1085	CVD_FEM	AA	AG	GG	1,51	0,88	0,5	20	11	3	16	15	9
1086	HELD_MAL_LIP	AA	AG	GG	1,97	1	0,44	7	10	3	5	18	13
1092	HELD_MAL_LIP	CC	CG	GG	0,94	0,4	2,38	2	5	13	4	21	12
1096	HELD_MAL_CC	GG	GT	TT	null	2,2	0,45	0	7	7	0	3	15
1096	CVD_MAL	GG	GT	TT	1,51	0,72	1,22	4	13	52	0	12	21
1101	HELD_FEM_EFF	CC	CT	TT	null	0	null	12	0	0	18	4	0
1204	HELD_MAL_LIP	AA	AG	GG	3,06	1,58	0,49	2	8	9	0	9	26
1204	HELD_ALL_LIP	AA	AG	GG	1,34	1,18	0,77	12	38	49	8	36	71
1504	HELD_ALL_CC	CC	CT	TT	0,5	1,79	0,78	5	27	12	12	12	15
1504	HELD_MAL_LIP	CC	CT	TT	0	1,6	1,14	0	12	7	8	17	12
1504	HELD_MAL_CC	CC	CT	TT	0,72	2,63	0,4	2	9	3	4	4	10
1504	HELD_FEM_CC	CC	CT	TT	0,4	1,44	1,13	3	18	9	8	8	5
1511	HELD_FEM_EFF	GG	GT	TT	0,33	3,38	0	3	9	0	14	7	1
1524	HELD_FEM_ADR3ULN	AA	AC	CC	0	1,51	0,89	0	16	22	8	23	51
1556	HELD_FEM_EFF	CC	CG	GG	null	3,36	0,3	0	7	5	0	3	19
1561	CVD_FEM	AA	AC	CC	1,59	0,73	0,41	23	12	1	17	19	4

BAYSNP	COMPARISON	GTYP1	GTYP2	CHVPE	RR1	RR2	RR3	FO1A	FO2A	FO1A'	FO2A'	FO1B	FO2B	FO1B'	FO2B'
1582	HELD_MAL_LIP	CC	CT	TT	0	0,78	1,89	0	5	15	5	12	20		
1638	HELD_FEM_CC	AA	AG	GG	0,56	0,62	1,73	1	8	22	2	11	9		
1653	CVD_MAL	GG	GT	TT	0,86	1,43	0,71	15	40	14	10	10	13		
1662	HELD_MAL_CC	CC	CT	TT	2,8	null	0,36	4	0	10	0	0	18		
1714	CVD_MAL	AA	AG	GG	0,48	0,98	1,23	3	26	37	6	14	14		
1722	HELD_FEM_ADRSULN	CC	CT	TT	2,8	0,41	0,93	8	5	5	14	43	24		
1757	HELD_FEM_EFF	AA	AG	GG	3	0,68	0,88	4	7	9	0	16	16		
1765	HELD_ALL_ADR3ULN	AA	AG	GG	0,67	0,36	2,71	1	7	55	4	48	97		
1765	HELD_ALL_ADR3ULN	AA	AG	GG	0,67	0,36	2,71	1	7	55	4	48	97		
1765	HELD_ALL_ADR5ULN	AA	AG	GG	null	0,31	3,64	0	3	24	4	48	97		
1765	HELD_ALL_ADR5ULN	AA	AG	GG	null	0,31	3,64	0	3	24	4	48	97		
1765	HELD_MAL_ADR3ULN	AA	AG	GG	0	0,26	4,23	0	2	24	2	21	47		
1765	HELD_MAL_ADR3ULN	AA	AG	GG	0	0,26	4,23	0	2	24	2	21	47		
1765	HELD_MAL_ADR5ULN	AA	AG	GG	0	0	null	0	0	10	2	21	47		
1765	HELD_MAL_ADR5ULN	AA	AG	GG	0	0	null	0	0	10	2	21	47		
1765	HELD_FEM_ADR3ULN	AA	AG	GG	1,05	0,41	2,23	1	5	31	2	27	50		
1765	HELD_FEM_ADR3ULN	AA	AG	GG	1,05	0,41	2,23	1	5	31	2	27	50		
1776	HELD_ALL_CC	AA	AG	GG	null	null	0	45	0	0	37	0	3		
1776	HELD_FEM_CC	AA	AG	GG	null	null	0	31	0	0	20	0	2		
1799	HELD_FEM_LIP2	CC	CT	TT	1,04	0,82	1,4	123	119	49	145	178	33		
1799	HELD_MAL_CC	CC	CT	TT	0,45	1,46	1,91	4	7	3	11	6	1		
1806	HELD_FEM_EFF	AA	AG	GG	3,96	0,35	0	11	1	0	14	6	2		
1837	HELD_FEM_LIP2	CC	CT	TT	1,17	0,77	1,32	164	108	32	166	167	22		
1837	HELD_ALL_LIP2	CC	CT	TT	1,18	0,83	1,04	334	223	50	322	308	52		
1837	HELD_ALL_ADR5ULN	CC	CT	TT	2,82	0,34	0,86	20	6	2	66	76	13		
1837	HELD_MAL_ADR	CC	CT	TT	1,45	0,7	0,96	37	33	7	21	44	7		

FAVS/P	COMPARISON	GTYP1	GTYP2	GTYP3	RR1	RR2	RR3	IQ1A	IQ2A	FO3A	FO1B	FO2B	FO3B
1837	HELD_MAL_LIP2	CC	CT	TT	1,19	0,89	0,77	170	115	18	156	141	30
1870	HELD_ALL_CC	CC	CT	TT	0,73	1,75	0,61	2	25	18	3	10	26
1870	HELD_FEM_CC	CC	CT	TT	0,85	1,75	0,58	1	20	10	1	7	14
1882	CVD_MAL	CC	CT	TT	1,06	0,76	1,59	21	37	11	9	25	0
1988	HELD_ALL_LIP	CC	CT	TT	1,26	0,95	0,64	52	39	9	48	48	20
2000	CVD_MAL	CC	TT	null	2,45	0,41	null	68	2	0	29	5	0
2000	CVD_ALL	CC	TT	null	1,98	0,51	null	101	4	0	65	9	0
2000	HELD_FEM_CC2	CC	TT	null	3,29	0,3	null	45	1	0	37	5	0
2000	HELD_MAL_HDL	CC	TT	null	2,00	0,50	0	20	0	0	20	2	0
2000	HELD_FEM_ADR	CC	TT	null	2,01	0,5	null	77	2	0	76	6	0
2000	HELD_MAL_CC	CC	TT	null	0,51	1,98	null	11	3	0	18	1	0
2071	CVD_ALL	AA	AG	GG	1,4	1,09	0,79	14	52	36	4	34	36
2078	HELD_MAL_LIP	GG	GT	TT	3,06	1,9	0,45	1	11	6	0	13	22
2085	HELD_FEM_VEFF	GG	GT	TT	2,5	0,79	0	6	4	0	3	7	4
2095	CVD_ALL	AG	GG	null	1,72	0,58	null	4	101	0	0	73	0
2119	HELD_MAL_LIP	AA	AG	null	0,35	2,83	null	3	17	0	16	21	0
2119	HELD_ALL_LIP	AA	AG	null	0,72	1,39	null	29	73	0	49	68	0
2119	HELD_FEM_EFF	AA	AG	null	0,38	2,67	null	3	9	0	13	9	0
2141	HELD_FEM_EFF	AA	AG	GG	0	3,25	0,42	0	6	6	2	2	18
2141	HELD_ALL_CC	AA	AG	GG	0	1,35	0,87	0	17	28	3	9	27
2182	HELD_FEM_EFF	AA	AG	GG	3,71	0,65	0	6	6	0	1	14	6
2234	HELD_MAL_LIP	GG	GT	TT	0	0,96	1,75	0	10	10	7	18	10
2281	HELD_FEM_VEFF	AA	AC	CC	0	1,04	2,13	0	5	4	4	7	2
2298	CVD_FEM	AA	AC	CC	2,23	0,57	1,31	4	10	21	0	20	18
2298	HELD_MAL_CC2	AA	AC	CC	0	0,7	1,65	0	8	21	2	12	14
2341	HELD_FEM_CC	CC	CT	TT	null	1,88	0,53	0	6	25	0	0	22

DAVSNP	COMPARISON	CTYPE1	CTYPE2	CTYPE3	RR1	RR2	RR3	FOLA	FOLA	FOLA	FOLB	FOLB	FOLB
2357	HELD_ALL_CC2	AA	AG	GG	2,03	0,76	1,1	5	18	51	0	25	46
2357	HELD_ALL_CC	AA	AG	GG	1,98	0,62	1,21	4	8	33	0	14	26
2357	HELD_MAL_LIP	AA	AG	GG		0,42	2,4	0	4	16	0	17	19
2357	HELD_FEM_CC	AA	AG	GG	1,81	0,57	1,13	4	4	23	0	7	15
2366	CVD_FEM	GG	GT	TT	1,51	1,12	0,55	12	14	7	8	15	17
2423	CVD_FEM	AA	AG	GG	1,48	1,08	0,45	16	13	4	12	14	13
2708	CVD_FEM	CC	CT	TT	3,67	0,27	null	28	1	0	33	7	0
2995	HELD_FEM_ADRSULN	AA	AC	CC	2,66	1,41	0,45	3	10	5	4	37	41
2995	HELD_FEM_UEFF	AA	AC	CC	0,67	0,68	1,57	2	20	32	5	40	30
3360	HELD_MAL_ADRSULN	GG	GT	TT	null	0	0	10	0	0	50	22	1
3464	HELD_ALL_CC	AA	AG	GG	0,43	0,83	1,61	3	15	27	9	17	14
3464	HELD_FEM_CC	AA	AG	GG	0,6	0,67	1,74	3	7	21	5	9	8
3689	HELD_FEM_EFF	CC	CG	GG	4	0,82	0	3	3	0	1	8	5
3975	HELD_FEM_UEFF	AA	AC	CC	0,37	0,83	1,5	2	24	30	10	38	27
3976	HELD_FEM_UEFF	AA	AG	GG	0,34	0,92	1,41	2	24	30	11	35	29
4206	HELD_FEM_ADR3ULN	AA	AT	TT	0,57	1,14	1,61	8	20	9	31	41	11
4838	HELD_FEM_VEFF	AA	AG	GG	3,27	0,35	0,56	7	2	1	3	8	3
4838	HELD_FEM_VEFF	AA	AG	GG	3,27	0,35	0,56	7	2	1	3	8	3
4838	HELD_FEM_VEFF	AA	AG	GG	3,27	0,35	0,56	7	2	1	3	8	3
4912	HELD_FEM_EFF	AA	AG	GG	2,33	0	0,56	7	0	5	5	2	13
4925	HELD_MAL_CC	AA	AC	CC	0,45	2,2	null	7	7	0	15	3	0
4966	HELD_MAL_ADR3ULN	AA	AG	GG	1,08	0,44	2,26	7	8	11	18	41	13
5014	HELD_ALL_ADR5ULN	AA	AG	GG	1,54	0,16	3,07	3	2	23	10	57	85
5014	HELD_FEM_ADR5ULN	AA	AG	GG	1,64	0,15	2,73	2	1	15	5	27	49
5296	CVD_FEM	AA	AG	GG	null	1,7	0,59	0	10	26	0	4	36
5296	HELD_FEM_EFF	AA	AG	GG	3	0,22	2,39	1	1	10	0	9	13

PAVSNP	COMPARISON	GTYP1	GTYP12	GTYP13	RR1	RR2	RR3	FQ1A	FQ2A	FQ3A	FQ1B	FQ2B	FQ3B
5296	CVD_ALL	AA	AG	GG	1,72	1,29	0,76	1	25	78	0	10	64
5298	HELD_FEM_EFF	CC	CT	TT	3,2	0,23	2,25	1	1	9	0	9	13
5298	CVD_ALL	CC	CT	TT	1,76	1,24	0,76	3	22	76	0	10	64
5298	CVD_FEM	CC	CT	TT	2,18	1,56	0,61	1	8	26	0	4	36
5320	HELD_FEM_EFF	AA	AG	GG	0,23	0,88	2,18	1	10	8	9	19	5
5361	CVD_MAL	AA	AC	CC	0,77	1,54	1,16	24	5	35	18	0	14
5457	HELD_FEM_EFF	AA	AG	GG	1,41	0	3,52	1	0	11	1	6	14
5704	HELD_MAL_LIP	CC	CT	TT	0,7	0,45	2,44	1	8	11	3	26	8
5704	CVD_MAL	CC	CT	TT	0,65	0,87	1,32	5	30	33	6	18	9
5717	HELD_FEM_ADR3ULN	AA	AG	GG	1,77	0,82	0,55	17	16	5	21	41	21
5717	HELD_ALL_ADR3ULN	AA	AG	GG	1,44	1,01	0,64	21	32	12	34	76	46
5959	HELD_ALL_CC	AA	AG	GG	1,81	0,85	0,59	16	20	7	4	21	13
5959	CVD_FEM	AA	AG	GG	3,6	0,8	0,27	4	4	1	0	7	6
5959	HELD_MAL_CC	AA	AG	GG	2,7	0,82	0,57	4	7	3	0	10	7
5959	HELD_MAL_ADR5ULN	AA	AG	GG	1,16	0,22	4,03	2	2	5	13	41	13
5959	HELD_FEM_ADR	AA	AG	GG	1,15	1,32	0,62	15	41	16	11	29	28
6162	HELD_ALL_ADR3ULN	CC	CG	GG	0,15	1,78	0,77	1	35	28	19	52	80
6162	HELD_ALL_ADR	CC	CG	GG	0,45	1,33	0,9	6	76	74	19	52	80
6162	HELD_ALL_ADR5ULN	CC	CG	GG	0	2,35	0,66	0	16	11	19	52	80
6162	HELD_MAL_ADR3ULN	CC	CG	GG	0	1,85	0,87	0	13	13	11	21	39
6162	HELD_FEM_ADR5ULN	CC	CG	GG	0	3,19	0,43	0	13	5	8	31	41
6162	HELD_MAL_ADR	CC	CG	GG	0,4	1,39	0,91	3	34	37	11	21	39
6236	HELD_ALL_ADR5ULN	CC	CT	TT	2,41	1,25	0,49	6	12	9	13	58	81
6236	HELD_MAL_ADR3ULN	CC	CT	TT	1,74	1,63	0,47	4	15	8	5	28	39
6236	HELD_MAL_ADR5ULN	CC	CT	TT	2,68	2,12	0,25	2	6	2	5	28	39
6236	HELD_ALL_ADR3ULN	CC	CT	TT	1,58	1,15	0,71	10	27	26	13	58	81

PAVSNP	COMPARISON	GTYP1	GTYP2	GTYP3	RR1	RR2	RR3	FQ1A	FQ2A	FQ3A	FQ1B	FQ2B	FQ3B
6482	HELD_MAL_HDL	AA	AG	GG	0,44	1,96	1,79	5	8	4	15	4	2
6482	HELD_ALL_LIP2	AA	AG	GG	0,87	1,16	1	340	238	41	436	226	47
6482	HELD_MAL_CC2	AA	AG	GG	1,93	0,66	0,47	18	7	2	10	12	6
6482	HELD_MAL_LIP2	AA	AG	GG	0,83	1,2	1,08	173	115	21	220	99	20
6498	CVD_FEM	AA	AG	GG	1,85	0,73	0	28	4	0	25	7	3
6744	HELD_ALL_ADRSULN	CC	CT	TT	2,27	1,54	0,47	4	13	9	9	56	84
7133	HELD_MAL_CC	CC	CG	GG	0,36	null	2,8	10	0	4	18	0	0
8021	CVD_FEM	AA	AG	GG	0,71	1,98	0,26	8	19	1	15	14	7
8060	CVD_FEM	AA	AG	GG	2,1	0,38	2,18	31	3	1	28	12	0
8060	HELD_FEM_HDL	AA	AG	GG	0,47	2,13	0	11	7	0	20	3	0
8210	HELD_FEM_EFF	AA	AG	GG	0,22	2,93	0,81	1	7	4	9	4	9
8592	HELD_FEM_VEFF	CC	CT	TT	0,7	1,32	0,86	15	92	43	25	68	50
8816	HELD_FEM_EFF	CC	CG	GG	2,22	1,17	0,36	4	7	2	0	5	6
8846	HELD_ALL_LIP	AA	AG	GG	1	1,18	0,4	57	47	3	62	42	12
8943	HELD_MAL_LIP	AA	AC	CC	1,89	0,78	0	15	5	0	20	12	5
9193	HELD_FEM_LIP	CC	CG	GG	1,54	0,65	null	72	11	0	60	20	0
9193	CVD_FEM	CC	CG	GG	0,59	1,59	2,14	28	7	1	37	3	0
9443	CVD_MAL	CC	CT	TT	1,55	1	0,85	9	25	35	0	12	21
9516	HELD_MAL_CC	AA	AG	GG	2,56	0,52	0,67	7	3	4	2	8	8
9698	HELD_MAL_ADR	AA	AG	GG	0,41	0	2,78	4	0	70	14	2	56
9698	HELD_MAL_ADR3ULN	AA	AG	GG	0	0	0	0	0	27	14	2	56
9698	HELD_FEM_EFF	AA	AG	GG	0,47	1,04	1,04	5	95	194	16	91	191
9698	HELD_MAL_ADR3ULN	AA	AG	GG	0	0	null	0	0	10	14	2	56
9698	CVD_ALL	AA	AG	GG	1,31	1,09	0,8	17	12	73	6	7	59
9849	HELD_FEM_CC	CC	CT	null	null	0	null	31	0	0	18	3	0
9849	HELD_MAL_LIP	CC	CT	null	0,42	2,38	null	15	5	0	35	2	0

BAYSNP	COMPARISON	GTTYPE1	GTTYPE2	GTTYPE3	RR1	RR2	RR3	FQ1A	FQ2A	FQ3A	FQ1B	FQ2B	FQ3B
9883	HELD_FEM_CC	AA	AG	GG	1,64	0,46	1,55	7	9	15	1	16	5
9883	HELD_ALL_CC	AA	AG	GG	1,37	0,58	1,42	9	15	21	4	24	11
10079	CVD_ALL	AA	AG	GG	1,74	0	0,72	4	0	99	0	1	72
10079	CVD_MAL	AA	AG	GG	1,53	null	0,65	4	0	64	0	0	34
10481	HELD_FEM_ADRSULN	AA	AT	TT	0,4	0,85	2,53	3	6	8	32	33	18
10542	HELD_FEM_VEFF	CC	CT	TT	2,42	0,47	1,86	1	6	47	0	21	54
10542	HELD_MAL_ADRSULN	CC	CT	TT	null	0	null	0	0	10	0	14	55
10600	HELD_FEM_VEFF	AA	AG	GG	null	0	null	0	0	21	0	4	29
10621	HELD_FEM_CC	CC	CT	TT	1,56	0,49	1,71	24	4	2	12	8	0
10745	HELD_ALL_ADRSULN	AA	AG	GG	3,09	0,86	0,72	5	10	12	7	61	80
10745	HELD_FEM_VEFF	AA	AG	GG	0,79	1,35	0,8	11	68	74	16	45	89
10747	HELD_MAL_ADR	CC	CT	TT	1,71	0,62	1,29	14	46	16	3	58	9
10747	CVD_ALL	CC	CT	TT	1,75	0,73	0,95	15	24	23	6	39	29
10747	HELD_MAL_ADRSULN	CC	CT	TT	2,24	0,45	1,77	4	16	7	3	58	9
10771	HELD_MAL_ADRSULN	CC	CG	GG	4,67	0,67	0,42	4	4	2	6	36	28
10771	HELD_FEM_VEFF	CC	CG	GG	1,14	1,07	0,86	52	118	114	40	105	131
10870	HELD_MAL_LIP	AA	AG	GG	0	2,26	0,64	0	11	9	5	9	23
10870	HELD_FEM_LIP	AA	AG	GG	0,9	0,65	1,5	7	18	57	8	30	39
10870	HELD_MAL_CC	AA	AG	GG	0	0,52	2,51	0	3	11	2	8	8
10870	HELD_ALL_CC	AA	AG	GG	0,45	0,83	1,47	2	13	30	6	15	19
10877	HELD_ALL_HDL	AA	AC	CC	0,61	0,53	2,00	0	0	9	1	5	9
10948	HELD_FEM_LIP	GG	GT	TT	0,58	1,45	1,04	16	51	17	31	33	15
10948	HELD_ALL_LIP	GG	GT	TT	0,62	1,35	1,1	22	60	22	44	50	21
10948	HELD_FEM_CC2	GG	GT	TT	0,59	1,67	0,83	9	28	7	17	16	9
10948	CVD_MAL	GG	GT	TT	0,69	1,09	1,23	12	39	18	12	17	5
11001	HELD_MAL_ADRSULN	CC	CT	TT	5,06	1,02	0,51	2	5	3	2	37	36

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WAYSNP	COMPARISON	GIYPE1	GIYPE2	GIYPE3	RR1	RR2	RR3	FO1A	FO2A	FO3A	FO1B	FO2B	FO3B
11073	HELD_MAL_ADRSULN	CC	CG	GG	2,71	1,32	0,33	3	4	2	9	25	34
11153	HELD_FEM_CC	CC	CT	TT	1,76	0,57	null	24	7	0	11	11	0
11210	HELD_MAL_CC	CC	CT	TT	0,4	2,5	null	9	5	0	18	1	0
11210	HELD_ALL_ADR3ULN	CC	CT	TT	0,6	1,79	0	47	16	0	125	17	2
11210	HELD_ALL_ADR	CC	CT	TT	0,8	1,32	0	122	31	0	125	17	2
11248	HELD_FEM_ADR	CC	CT	TT	1,57	0,59	1,08	56	19	6	38	36	5
11248	HELD_MAL_LIP	CC	CT	TT	2,65	0,38	null	15	3	0	19	15	0
11248	HELD_ALL_CC	CC	CT	TT	1,54	0,65	null	27	14	0	13	18	0
11372	HELD_MAL_LIP	AA	AG	GG	1,8	0,83	0,6	10	5	5	10	11	15
11449	HELD_FEM_CC	CC	CG	GG	1,73	0,41	2,05	1	4	26	0	10	12
11450	HELD_FEM_EFF	AA	AT	TT	1,3	1,06	0,87	28	114	147	16	107	167
11470	HELD_MAL_LIP	CC	CT	null	null	0	null	20	0	0	31	5	0
11472	HELD_MAL_LIP	AA	AT	null	null	0	null	20	0	0	30	5	0
11472	HELD_FEM_LIP	AA	AT	null	0,61	1,63	null	75	8	0	78	2	0
11487	HELD_MAL_ADRSULN	AT	TT	null	0	null	null	0	10	0	34	35	0
11487	HELD_MAL_ADR3ULN	AT	TT	null	0,4	2,5	null	6	21	0	34	35	0
11488	HELD_MAL_ADRSULN	CC	CG	GG	null	0	0	10	0	0	35	32	3
11488	HELD_FEM_UEFF	CC	CG	GG	0,79	1,02	2,57	29	20	5	49	28	0
11488	HELD_MAL_ADR3ULN	CC	CG	GG	2,48	0,3	1,52	20	4	2	35	32	3
11493	HELD_MAL_CC	AA	AG	GG	0	2,25	0,61	0	6	8	2	2	14
11502	HELD_MAL_ADR3ULN	CC	CT	TT	0	0,69	1,94	0	8	19	7	30	36
11502	HELD_MAL_ADRSULN	CC	CT	TT	0	0,4	3,55	0	2	8	7	30	36
11534	HELD_ALL_LIP	GG	GT	null	null	0	null	102	0	0	114	3	0
11537	CVD_FEM	AA	AG	GG	0,63	1,38	1,75	20	12	4	30	8	1
11537	HELD_FEM_EFF	AA	AG	GG	2,73	0,56	0	10	2	0	12	7	3
11560	HELD_FEM_EFF	AA	AG	GG	3		0,33	1	0	11	0	0	22

EASNP	COMPARISON	GTYPEN	GTYPEN2	GTYPEN3	RR1	RR2	RR3	FQ1A	FQ2A	FQ3A	FQ1B	FQ2B	FQ3B
11578	HELD_FEM_LIP	CC	CT	null	4,62	0,22	null	60	1	0	57	8	0
11578	CVD_FEM	CC	CT	null	0,41	2,44	null	27	3	0	39	0	0
11594	HELD_FEM_ADR3ULN	CC	CT	TT	0	0	null	0	0	37	2	6	72
11594	HELD_ALL_ADR3ULN	CC	CT	TT	0	0	null	0	0	27	2	16	133
11594	HELD_ALL_CC	CC	CT	TT	null	1,6	0,62	0	10	35	0	3	38
11594	HELD_ALL_ADR	CC	CT	TT	0,66	0,58	1,71	1	7	147	2	16	133
11594	HELD_FEM_ADR5ULN	CC	CT	TT	0	0	null	0	0	18	2	6	72
11624	HELD_ALL_CC	CC	CT	TT	1	0,75	2,11	21	15	6	20	20	0
11624	HELD_MAL_CC	CC	CT	TT	1,32	0,33	2,8	8	2	3	9	9	0
11624	HELD_FEM_EFF	CC	CT	TT	2,5	0,63	0	10	2	0	12	6	3
11627	HELD_ALL_CC	CC	CT	TT	0,86	0,86	2,05	20	18	7	21	19	0
11627	HELD_MAL_CC	CC	CT	TT	1	0,58	2,64	7	4	3	9	9	0
11627	HELD_FEM_EFF	CC	CT	TT	2,73	0,56	0	10	2	0	12	7	3
11644	HELD_MAL_ADR5ULN	AA	AG	GG	0	0,45	3,26	0	2	8	7	26	35
11650	HELD_FEM_EFF	AA	AG	GG	1,07	0,8	1,21	26	105	160	23	135	132
11654	HELD_ALL_ADR5ULN	AA	AG	GG	2,59	0,24	1,48	7	3	15	14	56	66
11654	HELD_FEM_ADR5ULN	AA	AG	GG	2,81	0,12	1,65	5	1	9	8	31	32
11654	HELD_FEM_ADR3ULN	AA	AG	GG	1,81	0,48	1,25	8	7	17	8	31	32
11654	HELD_ALL_ADR3ULN	AA	AG	GG	1,83	0,66	1,02	12	15	26	14	56	66
11655	HELD_ALL_ADR5ULN	AA	AC	CC	1,56	0,24	2,3	16	3	7	72	59	17
11655	HELD_FEM_ADR5ULN	AA	AC	CC	2,03	0,11	2,11	11	1	5	35	34	11
11655	HELD_FEM_ADR3ULN	AA	AC	CC	1,34	0,45	1,64	19	7	9	35	34	11
11656	HELD_MAL_LIP	CC	CT	TT	0,53	0,96	2,57	6	8	6	19	15	2
11656	HELD_FEM_EFF	CC	CT	TT	2,57	0,56	0	7	5	0	5	14	3
11656	HELD_ALL_LIP	CC	CT	TT	0,79	1,01	1,5	35	49	18	51	54	9
11825	HELD_MAL_ADR5ULN	AA	AG	null	0,25	4	null	6	3	0	58	5	0

WAYSNP	COMPARISON	GTYPED1	GTYPED2	GTYPED3	RR1	RR2	RR3	Q1A	Q2A	Q3A	Q1B	Q2B	Q3B
11914	HELD_MAL_ADRSULN	AA	AT	TT	0,11	0	9,83	1	0	8	41	1	27
11914	HELD_ALL_ADRSULN	AA	AT	TT	0,45	1,43	1,48	6	12	9	63	52	36
12008	HELD_FEM_EFF	CC	CT	null	0,72	1,38	null	251	27	0	264	13	0
12008	HELD_ALL_ADRSULN	CC	CT	null	null	0	null	24	0	0	122	12	0
12097	HELD_ALL_ADRSULN	AG	GG	null	2,66	0,38	null	6	22	0	11	144	0
12097	HELD_FEM_ADR3ULN	AG	GG	null	2,05	0,49	null	7	31	0	5	78	0
12097	HELD_MAL_ADRSULN	AG	GG	null	3,48	0,29	null	3	7	0	6	66	0
12097	HELD_ALL_ADR3ULN	AG	GG	null	1,77	0,56	null	10	53	0	11	144	0
12366	HELD_FEM_UEFF	AA	AG	GG	1,33	1,02	0	32	18	0	39	26	9
12366	HELD_ALL_ADRSULN	AA	AG	GG	1,82	0,34	2,26	18	4	3	85	59	7
12619	HELD_MAL_ADRSULN	AG	GG	null	8,89	0,11	null	1	9	0	0	71	0
12619	HELD_ALL_ADRSULN	AG	GG	null	4,67	0,21	null	2	25	0	1	150	0
13025	HELD_ALL_ADRSULN	AA	AC	CC	1,12	0,51	2,38	13	8	7	65	71	15
13191	HELD_FEM_LIP	AA	AG	GG	0,71	0,71	1,55	6	30	47	10	42	27
13191	HELD_MAL_CC	AA	AG	GG	2,5	1,67	0,43	2	7	5	0	5	13
13191	HELD_ALL_LIP	AA	AG	GG	0,65	0,81	1,38	6	39	56	13	55	46
13937	HELD_FEM_ADRSULN	AA	AC	CC	0,36	1,91	2,53	4	11	2	42	38	3
900002	CVD_FEM	GG	GT	TT	1,65	1,29	0,64	5	13	16	2	11	27
900013	CVD_FEM	CC	CG	GG	1,7	0,47	1,34	20	9	6	13	23	4
900013	CVD_ALL	CC	CG	GG	1,32	0,7	1,16	58	34	12	29	39	6
900025	CVD_MAL	GG	GT	TT	0,73	0,88	1,3	7	27	32	7	17	10
900032	CVD_FEM	CC	CT	TT	2,48	0,22	2,54	23	1	1	28	9	0
900045	HELD_FEM_EFF	CC	CT	TT	0,42	0,48	2,67	1	2	9	5	8	9
900065	CVD_FEM	AA	AC	CC	1,91	0,7	0	22	10	0	16	18	5
900065	CVD_MAL	AA	AC	CC	1,29	0,72	1,53	25	30	4	7	22	0
900065	CVD_ALL	AA	AC	CC	1,36	0,77	0,77	47	40	4	23	40	5

BAVSNP	COMPARISON	GTYP1	GTYP2	GTYP3	RM	RR2	RR3	IQ1A	IQ1A	IQ1A	IQ2A	IQ2B	IQ3B
900078	HELD_ALL_ADR3ULN	AA	AG	GG	0,56	1,79	null	52	12	0	142	13	0
900078	HELD_ALL_ADR5ULN	AA	AG	GG	0,41	2,45	null	21	6	0	142	13	0
900078	HELD_FEM_ADR3ULN	AA	AG	GG	0,49	2,05	null	31	7	0	78	5	0
900082	HELD_FEM_ADR3ULN	AA	AG	GG	1	0,49	1,9	8	9	18	17	36	21
900082	HELD_FEM_ADR5ULN	AA	AG	GG	0,76	0,39	2,76	3	4	10	17	36	21
900096	CVD_ALL	AA	AG	GG	0,74	1,35	1,15	60	37	4	55	15	2
900107	HELD_MAL_ADR5ULN	CC	CT	TT	0	0,52	3,06	0	2	8	9	25	39
900115	HELD_MAL_ADR5ULN	AA	AG	GG	0,24	0,78	4,6	1	4	4	27	37	8
900115	HELD_FEM_EFF	AA	AG	GG	1,47	0,56	1,8	22	14	4	17	28	1
900121	HELD_MAL_ADR	GG	GT	TT	0,46	1,42	0,95	5	37	24	15	26	26
900173	CVD_ALL	GG	GT	TT	0,5	1,35	1,38	5	7	11	11	4	7
10000002	HELD_FEM_EFF	AA	AG	GG	2,67	0,8	0	9	3	0	9	7	6
10000006	HELD_FEM_CC	AA	AG	GG	3,35	0,26	0,56	28	2	1	11	9	2
10000006	HELD_ALL_CC	AA	AG	GG	2,52	0,41	0,45	39	4	1	23	12	3
10000014	HELD_ALL_CC	AA	AC	CC	2,18	0,33	1,26	40	3	2	26	12	1
10000014	HELD_FEM_CC	AA	AC	CC	2,17	0,34	1,73	28	2	1	15	7	0
10000025	HELD_MAL_LIP	CC	CT	TT	1,17	1,41	0	9	11	0	14	15	7

Table 6b: Correlation of PA SNP alleles to relative risk

For diagnostic conclusions to be drawn from genotyping a particular patient we calculated the relative risks RR_1 , and RR_2 for the two possible alleles of each SNP. Given the allele frequencies as

	allele1	allele2
case	N11	N12
control	N21	N22

we calculate

$$\frac{N11 \cdot N22}{N12 \cdot N21}$$

$$\frac{N11 \cdot N22}{N12 \cdot N21}$$

Here, the *case* and *control* populations represent any case-control-group pair, or bad(case)-good(control)-group pair, respectively (due to their increased response to statins, 'high responders' are treated as a case cohort, whereas 'low responders' are treated as the respective control cohort). A value $RR_1 > 1$, and $RR_2 > 1$ indicates an increased risk for individuals carrying allele 1, and allele2, respectively. For example, $RR_1 = 3$ indicates a 3-fold risk of an individual carrying allele 1 as compared to individuals not carrying allele 1 (a detailed description of relative risk calculation and statistics can be found in (Biostatistics, L. D. Fisher and G. van Belle, Wiley Interscience 1993)). The baySNP number refers to an internal numbering of the PA SNPs and can be found in the sequence listing. null: not defined.

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BAVSNP	ADUELE1	ADUELE2	COMPARISON	RR1	RR2	SIZEA	FREQ1A	FREQ2A	SIZEB	FREQ1B	FREQ2B
28	C	T	HELD_FEM_EFF	0,42	2,39	12	4	20	22	18	26
29	A	G	HELD_ALL_HDL	2,01	0,5	10	12	8	15	7	23
29	A	G	HELD_MAL_ADR3ULN	1,63	0,61	26	33	19	72	68	76
29	A	G	HELD_MAL_ADR5ULN	2,6	0,38	9	13	5	72	68	76
52	C	G	HELD_FEM_EFF	1,84	0,54	18	24	12	31	27	35
56	A	G	HELD_FEM_EFF	2,29	0,44	12	5	19	22	2	42
89	A	G	HELD_ALL_CC	null	0	45	90	0	40	77	3
90	C	T	HELD_FEM_CC	0,78	1,27	31	29	33	22	27	17
99	C	T	HELD_FEM_LIP	1,02	0,98	82	54	110	80	51	109
140	C	T	HELD_FEM_EFF	null	0	12	24	0	21	4	38
152	A	G	HELD_FEM_EFF	0,51	1,96	12	12	12	22	33	11
214	A	G	HELD_ALL_LIP	1	1	97	156	38	113	182	44
214	A	G	HELD_FEM_LIP	1,09	0,92	81	131	31	78	122	34
221	C	G	HELD_ALL_CC	0,88	1,13	45	26	64	39	27	51
221	C	G	HELD_FEM_CC	0,77	1,3	31	17	45	22	18	26
224	C	T	HELD_FEM_LIP	0,79	1,27	79	110	48	79	125	33
224	C	T	HELD_MAL_LIP	2,28	0,44	20	35	5	37	51	23
294	C	T	HELD_ALL_CC	0,81	1,24	45	56	34	40	58	22
307	C	T	CVD_FEM	0,57	1,75	36	19	53	38	38	38
307	C	T	HELD_ALL_LIP	1,2	0,83	102	70	134	117	63	171
411	A	T	HELD_ALL_HDL	1,56	0,64	10	17	3	15	18	12
449	C	G	HELD_MAL_LIP	0,41	2,47	20	3	37	37	16	58
466	C	T	CVD_FEM	0,7	1,43	35	27	43	40	44	36
472	A	G	HELD_FEM_EFF	null	0	11	22	0	22	12	32
542	A	G	HELD_MAL_CC	2,79	0,36	14	12	16	19	2	36
542	A	G	HELD_MAL_HDL	3,66	0,27	21	14	28	27	3	51

BAYSNP	ALLELE1	ALLELE2	COMPARISON	RR1	RR2	SIZEA	FREQ1A	FREQ2A	SIZEB	FREQ1B	FREQ2B
542	A	G	HELD_ALL_ADR	1,19	0,84	159	53	265	154	37	271
542	A	G	HELD_FEM_HDL	0,66	1,51	23	2	44	32	10	54
739	C	G	HELD_ALL_CC	0,73	1,37	45	39	51	40	48	32
821	A	C	HELD_MAL_LIP2	1,12	0,9	309	180	438	349	174	524
821	A	C	HELD_FEM_VEFF	0,42	2,4	10	4	16	14	14	14
1005	A	G	HELD_MAL_CC	2,7	0,37	14	26	2	18	27	9
1055	A	T	HELD_MAL_CC	0,56	1,77	9	3	15	12	8	16
1056	A	G	HELD_FEM_EFF	1,01	0,99	24	30	18	33	41	25
1085	A	G	HELD_MAL_LIP	0,57	1,74	20	17	23	36	46	26
1085	A	G	CVD_FEM	1,53	0,65	34	51	17	40	47	33
1086	A	G	HELD_MAL_LIP	1,73	0,58	20	24	16	36	28	44
1092	C	G	HELD_MAL_LIP	0,58	1,72	20	9	31	37	29	45
1096	G	T	HELD_MAL_CC	1,8	0,56	14	7	21	18	3	33
1096	G	T	CVD_MAL	0,93	1,08	69	21	117	33	12	54
1101	C	T	HELD_FEM_EFF	null	0	12	24	0	22	40	4
1204	A	G	HELD_MAL_LIP	1,91	0,52	19	12	26	35	9	61
1204	A	G	HELD_ALL_LIP	1,26	0,8	99	62	136	115	52	178
1504	C	T	HELD_ALL_CC	0,92	1,08	44	37	51	39	36	42
1504	C	T	HELD_MAL_LIP	0,69	1,46	19	12	26	37	33	41
1504	C	T	HELD_MAL_CC	1,35	0,74	14	13	15	18	12	24
1504	C	T	HELD_FEM_CC	0,75	1,33	30	24	36	21	24	18
1511	G	T	HELD_FEM_EFF	0,6	1,67	12	15	9	22	35	9
1524	A	C	HELD_FEM_ADR3ULN	0,9	1,11	38	16	60	82	39	125
1556	C	G	HELD_FEM_EFF	2,39	0,42	12	7	17	22	3	41
1561	A	C	CVD_FEM	1,53	0,65	36	58	14	40	53	27
1582	C	T	HELD_MAL_LIP	0,46	2,17	20	5	35	37	22	52
1638	A	G	HELD_FEM_CC	0,62	1,6	31	10	52	22	15	29

SNP	ALLELE1	ALLELE2	COMPARISON	R1	R2	SIZEA	FREQ1A	FREQ2A	SIZEB	FREQ1B	FREQ2B
1653	G	T	CVD_MAL	1,07	0,93	69	70	68	33	30	36
1662	C	T	HELD_MAL_CC	0,18	5,5	14	8	20	18	36	0
1714	A	G	CVD_MAL	0,78	1,28	66	32	100	34	26	42
1722	C	T	HELD_FEM_ADR5ULN	1,61	0,62	18	21	15	81	71	91
1757	A	G	HELD_FEM_EFF	1,41	0,71	20	15	25	32	16	48
1765	A	G	HELD_ALL_ADR3ULN	0,42	2,35	63	9	117	149	56	242
1765	A	G	HELD_ALL_ADR3ULN	0,42	2,35	63	9	117	149	56	242
1765	A	G	HELD_ALL_ADR5ULN	0,29	3,42	27	3	51	149	56	242
1765	A	G	HELD_ALL_ADR5ULN	0,29	3,42	27	3	51	149	56	242
1765	A	G	HELD_MAL_ADR3ULN	0,24	4,09	26	2	50	70	25	115
1765	A	G	HELD_MAL_ADR3ULN	0,24	4,09	26	2	50	70	25	115
1765	A	G	HELD_MAL_ADR5ULN	null	0	10	20	0	70	25	115
1765	A	G	HELD_MAL_ADR5ULN	null	0	10	20	0	70	25	115
1765	A	G	HELD_FEM_ADR3ULN	0,53	1,87	37	7	67	79	31	127
1765	A	G	HELD_FEM_ADR3ULN	0,53	1,87	37	7	67	79	31	127
1776	A	G	HELD_ALL_CC	null	0	45	90	0	40	74	6
1776	A	G	HELD_FEM_CC	null	0	31	62	0	22	40	4
1799	C	T	HELD_FEM_LIP2	0,93	1,07	291	365	217	356	468	244
1799	C	T	HELD_MAL_CC	0,56	1,77	14	15	13	18	28	8
1806	A	G	HELD_FEM_EFF	4,44	0,23	12	23	1	22	34	10
1837	C	T	HELD_FEM_LIP2	1,04	0,96	304	436	172	355	499	211
1837	C	T	HELD_ALL_LIP2	1,1	0,91	607	891	323	682	952	412
1837	C	T	HELD_ALL_ADR5ULN	2,03	0,49	28	46	10	155	208	102
1837	C	T	HELD_MAL_ADR	1,24	0,81	77	107	47	72	86	58
1837	C	T	HELD_MAL_LIP2	1,17	0,86	303	455	151	327	453	201
1870	C	T	HELD_ALL_CC	1,3	0,77	45	29	61	39	16	62
1870	C	T	HELD_FEM_CC	1,33	0,75	31	22	40	22	9	35

BAVENP	ALLELE1	ALLELE2	COMPARISON	RR1	RR2	SIZEA	FRQ01A	FRQ02A	SIZEB	FRQ01B	FRQ02B
1882	C	T	CVD_MAL	0,92	1,08	69	79	59	34	43	25
1988	C	T	HELD_ALL_LIP	1,27	0,79	100	143	57	116	144	88
2000	C	T	CVD_MAL	2,45	0,41	70	136	4	34	58	10
2000	C	T	CVD_ALL	1,98	0,51	105	202	8	74	130	18
2000	C	T	HELD_FEM_CC2	3,29	0,3	46	90	2	42	74	10
2000	C	T	HELD_MAL_HDL	2	0,5	20	40	0	22	40	4
2000	C	T	HELD_FEM_ADR	2,01	0,5	79	154	4	82	152	12
2000	C	T	HELD_MAL_CC	0,51	1,98	14	22	6	19	36	2
2071	A	G	CVD_ALL	1,22	0,82	102	80	124	74	42	106
2078	G	T	HELD_MAL_LIP	1,74	0,58	18	13	23	35	13	57
2085	G	T	HELD_FEM_VEFF	2,62	0,38	10	16	4	14	13	15
2095	A	G	CVD_ALL	0,03	37,5	105	4	206	73	146	0
2119	A	G	HELD_MAL_LIP	0,68	1,48	20	23	17	37	53	21
2119	A	G	HELD_ALL_LIP	0,85	1,17	102	131	73	117	166	68
2119	A	G	HELD_FEM_EFF	0,6	1,67	12	15	9	22	35	9
2141	A	G	HELD_FEM_EFF	1,56	0,64	12	6	18	22	6	38
2141	A	G	HELD_ALL_CC	0,99	1,01	45	17	73	39	15	63
2182	A	G	HELD_FEM_EFF	2,82	0,35	12	18	6	21	16	26
2234	G	T	HELD_MAL_LIP	0,54	1,85	20	10	30	35	32	38
2281	A	C	HELD_FEM_VEFF	0,46	2,17	9	5	13	13	15	11
2298	A	C	CVD_FEM	0,98	1,02	35	18	52	38	20	56
2298	A	C	HELD_MAL_CC2	0,6	1,67	29	8	50	28	16	40
2341	C	T	HELD_FEM_CC	0,12	8,33	31	6	56	22	44	0
2357	A	G	HELD_ALL_CC2	1,04	0,96	74	28	120	71	25	117
2357	A	G	HELD_ALL_CC	1,01	0,99	45	16	74	40	14	66
2357	A	G	HELD_MAL_LIP	0,48	2,08	20	4	36	36	17	55
2357	A	G	HELD_FEM_CC	1,1	0,91	31	12	50	22	7	37

BAYSNP	ADJLE1	ALLELE2	COMPARISON	RM	RR2	SIZEA	FREQ1A	FREQ2A	SIZEB	FREQ1B	FREQ2B
2366	G	T	CVD_FEM	1,51	0,66	33	38	28	40	31	49
2423	A	G	CVD_FEM	1,57	0,63	33	45	21	39	38	40
2708	C	T	CVD_FEM	3,51	0,29	29	57	1	40	73	7
2995	A	C	HELD_FEM_ADRSULN	1,82	0,55	18	16	20	82	45	119
2995	A	C	HELD_FEM_UEFF	0,71	1,41	54	24	84	75	50	100
3360	G	T	HELD_MAL_ADRSULN	null	0	10	20	0	73	122	24
3464	A	G	HELD_ALL_CC	0,62	1,61	45	21	69	40	35	45
3464	A	G	HELD_FEM_CC	0,61	1,63	31	13	49	22	19	25
3689	C	G	HELD_FEM_EFF	3,32	0,3	6	9	3	14	10	18
3975	A	C	HELD_FEM_UEFF	0,68	1,47	56	28	84	75	58	92
3976	A	G	HELD_FEM_UEFF	0,69	1,44	56	28	84	75	57	93
4206	A	T	HELD_FEM_ADRSULN	0,69	1,45	37	36	38	83	103	63
4838	A	G	HELD_FEM_VEFF	2,4	0,42	10	16	4	14	14	14
4838	A	G	HELD_FEM_VEFF	2,4	0,42	10	16	4	14	14	14
4838	A	G	HELD_FEM_VEFF	2,4	0,42	10	16	4	14	14	14
4912	A	G	HELD_FEM_EFF	2,05	0,49	12	14	10	20	12	28
4925	A	C	HELD_MAL_CC	0,56	1,8	14	21	7	18	33	3
4966	A	G	HELD_MAL_ADRSULN	0,72	1,39	26	22	30	72	77	67
5014	A	G	HELD_ALL_ADRSULN	0,54	1,85	28	8	48	152	77	227
5014	A	G	HELD_FEM_ADRSULN	0,6	1,67	18	5	31	81	37	125
5296	A	G	CVD_FEM	1,59	0,63	36	10	62	40	4	76
5296	A	G	HELD_FEM_EFF	0,67	1,5	12	3	21	22	9	35
5296	A	G	CVD_ALL	1,29	0,78	104	27	181	74	10	138
5298	C	T	HELD_FEM_EFF	0,71	1,41	11	3	19	22	9	35
5298	C	T	CVD_ALL	1,32	0,76	101	28	174	74	10	138
5298	C	T	CVD_FEM	1,62	0,62	35	10	60	40	4	76
5320	A	G	HELD_FEM_EFF	0,52	1,93	19	12	26	33	37	29

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BAISNP	ALLELE1	ALLELE2	COMPARISON	RR1	RR2	SIZEA	TRFO1A	TRFO1A	TRFO1A	SIZEB	TRFO1B	TRFO2B
5361	A	C	CVD_MAL	0,82	1,22	64	53	75	32	36		28
5457	A	G	HELD_FEM_EFF	0,51	1,96	12	2	22	21	8		34
5704	C	T	HELD_MAL_LIP	0,57	1,75	20	10	30	37	32		42
5704	C	T	CVD_MAL	0,79	1,27	68	40	96	33	30		36
5717	A	G	HELD_FEM_ADR3ULN	1,58	0,63	38	50	26	83	83		83
5717	A	G	HELD_ALL_ADR3ULN	1,36	0,74	65	74	56	156	144		168
5959	A	G	HELD_ALL_CC	1,53	0,65	43	52	34	38	29		47
5959	A	G	CVD_FEM	2,63	0,38	9	12	6	13	7		19
5959	A	G	HELD_MAL_CC	1,71	0,59	14	15	13	17	10		24
5959	A	G	HELD_MAL_ADR3ULN	0,54	1,85	9	6	12	67	67		67
5959	A	G	HELD_FEM_ADR	1,26	0,79	72	71	73	68	51		85
6162	C	G	HELD_ALL_ADR3ULN	0,97	1,03	64	37	91	151	90		212
6162	C	G	HELD_ALL_ADR	0,96	1,04	156	88	224	151	90		212
6162	C	G	HELD_ALL_ADR5ULN	0,99	1,01	27	16	38	151	90		212
6162	C	G	HELD_MAL_ADR3ULN	0,82	1,22	26	13	39	71	43		99
6162	C	G	HELD_FEM_ADR5ULN	1,28	0,78	18	13	23	80	47		113
6162	C	G	HELD_MAL_ADR	0,92	1,08	74	40	108	71	43		99
6236	C	T	HELD_ALL_ADR5ULN	1,85	0,54	27	24	30	152	84		220
6236	C	T	HELD_MAL_ADR3ULN	1,67	0,6	27	23	31	72	38		106
6236	C	T	HELD_MAL_ADR5ULN	2,42	0,41	10	10	10	72	38		106
6236	C	T	HELD_ALL_ADR3ULN	1,36	0,74	63	47	79	152	84		220
6482	A	G	HELD_MAL_HDL	0,51	1,96	17	18	16	21	34		8
6482	A	G	HELD_ALL_LIP2	0,91	1,1	619	918	320	709	1098		320
6482	A	G	HELD_MAL_CC2	1,82	0,55	27	43	11	28	32		24
6482	A	G	HELD_MAL_LIP2	0,87	1,15	309	461	157	339	539		139
6498	A	G	CVD_FEM	2,18	0,46	32	60	4	35	57		13
6744	C	T	HELD_ALL_ADR5ULN	1,82	0,55	26	21	31	149	74		224

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BAYSNP	ALLELE1	ALLELE2	COMPARISON	RRI	R2	SIZEA	FREQ1A	FREQ2A	SIZEB	FREQ1B	FREQ2B
7133	C	G	HELD_MAL_CC	0,36	2,8	14	20	8	18	36	0
8021	A	G	CVD_FEM	1,03	0,97	28	35	21	36	44	28
8060	A	G	CVD_FEM	1,66	0,6	35	65	5	40	68	12
8060	A	G	HELD_FEM_HDL	0,5	1,99	18	29	7	23	43	3
8210	A	G	HELD_FEM_EFF	0,72	1,4	12	9	15	22	22	22
8592	C	T	HELD_FEM_VEFF	0,99	1,01	150	122	178	143	118	168
8816	C	G	HELD_FEM_EFF	1,91	0,52	13	15	11	11	5	17
8846	A	G	HELD_ALL_LIP	1,11	0,9	107	161	53	116	166	66
8943	A	C	HELD_MAL_LIP	2,17	0,46	20	35	5	37	52	22
9193	C	G	HELD_FEM_LIP	1,48	0,68	83	155	11	80	140	20
9193	C	G	CVD_FEM	0,6	1,67	36	63	9	40	77	3
9443	C	T	CVD_MAL	1,23	0,82	69	43	95	33	12	54
9516	A	G	HELD_MAL_CC	1,87	0,54	14	17	11	18	12	24
9698	A	G	HELD_MAL_ADR	0,38	2,62	74	8	140	72	30	114
9698	A	G	HELD_MAL_ADR3ULN	null	0	27	54	0	72	30	114
9698	A	G	HELD_FEM_EFF	0,91	1,1	294	105	483	298	123	473
9698	A	G	HELD_MAL_ADR5ULN		0	10	20	0	72	30	114
9698	A	G	CVD_ALL	1,27	0,79	102	46	158	72	19	125
9849	C	T	HELD_FEM_CC	null	0	31	62	0	21	39	3
9849	C	T	HELD_MAL_LIP	0,46	2,18	20	35	5	37	72	2
9883	A	G	HELD_FEM_CC	0,93	1,07	31	23	39	22	18	26
9883	A	G	HELD_ALL_CC	0,92	1,09	45	33	57	39	32	46
10079	A	G	CVD_ALL	1,54	0,65	103	8	198	73	1	145
10079	A	G	CVD_MAL	0,11	9,5	68	8	128	34	68	0
10481	A	T	HELD_FEM_ADR5ULN	0,46	2,2	17	12	22	83	97	69
10542	C	T	HELD_FEM_VEFF	0,63	1,58	54	8	100	75	21	129
10542	C	T	HELD_MAL_ADR5ULN	null	0	10	20	0	69	14	124

BAVSNP	ALLELE1	ALLELE2	COMPARISON	RR1	RR2	SIZEA	FRQ1A	FRQ2A	SIZEB	FRQ1B	FRQ2B
10600	A	G	HELD_FEM_EFF	null	0	21	42	0	33	4	62
10621	C	T	HELD_FEM_CC	1,24	0,81	30	52	8	20	32	8
10745	A	G	HELD_ALL_ADRSULN	1,58	0,63	27	20	34	148	75	221
10745	A	G	HELD_FEM_VEFF	1,1	0,91	153	90	216	150	77	223
10747	C	T	HELD_MAL_ADR	1,06	0,94	76	74	78	70	64	76
10747	C	T	CVD_ALL	1,23	0,82	62	54	70	74	51	97
10747	C	T	HELD_MAL_ADR3ULN	0,96	1,04	27	24	30	70	64	76
10771	C	G	HELD_MAL_ADRSULN	2,5	0,4	10	12	8	70	48	92
10771	C	G	HELD_FEM_EFF	1,12	0,89	284	222	346	276	185	367
10870	A	G	HELD_MAL_LIP	1,06	0,94	20	11	29	37	19	55
10870	A	G	HELD_FEM_LIP	0,75	1,34	82	32	132	77	46	108
10870	A	G	HELD_MAL_CC	0,39	2,55	14	3	25	18	12	24
10870	A	G	HELD_ALL_CC	0,67	1,5	45	17	73	40	27	53
10877	A	C	HELD_ALL_HDL	3,57	0,28	9	18	0	15	7	23
10948	G	T	HELD_FEM_LIP	0,81	1,23	84	83	85	79	95	63
10948	G	T	HELD_ALL_LIP	0,81	1,23	104	104	104	115	138	92
10948	G	T	HELD_FEM_CC2	0,87	1,15	44	46	42	42	50	34
10948	G	T	CVD_MAL	0,82	1,21	69	63	75	34	41	27
11001	C	T	HELD_MAL_ADRSULN	1,96	0,51	10	9	11	75	41	109
11073	C	G	HELD_MAL_ADRSULN	2,38	0,42	9	10	8	68	43	93
11153	C	T	HELD_FEM_CC	1,61	0,62	31	55	7	22	33	11
11210	C	T	HELD_MAL_CC	0,46	2,17	14	23	5	19	37	1
11210	C	T	HELD_ALL_ADR3ULN	0,67	1,48	63	110	16	144	267	21
11210	C	T	HELD_ALL_ADR	0,85	1,17	153	275	31	144	267	21
11248	C	T	HELD_FEM_ADR	1,34	0,75	81	131	31	79	112	46
11248	C	T	HELD_MAL_LIP	2,3	0,43	18	33	3	34	53	15
11248	C	T	HELD_ALL_CC	1,39	0,72	41	68	14	31	44	18

BAYSNP	ALLELE1	ALLELE2	COMPARISON	RR1	RR2	SIZEA	FREQ1A	FREQ2A	SIZEB	FREQ1B	FREQ2B
11372	A	G	HELD_MAL_LIP	1,67	0,6	20	25	15	36	31	41
11449	C	G	HELD_FEM_CC	0,6	1,66	31	6	56	22	10	34
11450	A	T	HELD_FEM_EFF	1,14	0,87	289	170	408	290	139	441
11470	C	T	HELD_MAL_LIP	null	0	20	40	0	36	67	5
11472	A	T	HELD_MAL_LIP	null	0	20	40	0	35	65	5
11472	A	T	HELD_FEM_LIP	0,63	1,6	83	158	8	80	158	2
11487	A	T	HELD_MAL_ADRSULN	null	0	10	20	0	69	34	104
11487	A	T	HELD_MAL_ADR3ULN	0,48	2,11	27	6	48	69	34	104
11488	C	G	HELD_MAL_ADRSULN	null	0	10	20	0	70	102	38
11488	C	G	HELD_FEM_UEFF	0,74	1,35	54	78	30	77	126	28
11488	C	G	HELD_MAL_ADR3ULN	1,73	0,58	26	44	8	70	102	38
11493	A	G	HELD_MAL_CC	1,18	0,85	14	6	22	18	6	30
11502	C	T	HELD_MAL_ADR3ULN	0,49	2,02	27	8	46	73	44	102
11502	C	T	HELD_MAL_ADRSULN	0,29	3,45	10	2	18	73	44	102
11534	G	T	HELD_ALL_LIP	null	0	102	204	0	117	231	3
11537	A	G	CVD_FEM	0,65	1,54	36	52	20	39	68	10
11537	A	G	HELD_FEM_EFF	3,11	0,32	12	22	2	22	31	13
11560	A	G	HELD_FEM_EFF	0,04	23	12	2	22	22	44	0
11578	C	T	HELD_FEM_LIP	4,48	0,22	61	121	1	65	122	8
11578	C	T	CVD_FEM	0,42	2,37	30	57	3	39	78	0
11594	C	T	HELD_FEM_ADR3ULN	null	0	37	74	0	80	10	150
11594	C	T	HELD_ALL_ADRSULN	null	0	27	54	0	151	20	282
11594	C	T	HELD_ALL_CC	1,53	0,65	45	10	80	41	3	79
11594	C	T	HELD_ALL_ADR	0,6	1,66	155	9	301	151	20	282
11594	C	T	HELD_FEM_ADRSULN	null	0	18	36	0	80	10	150
11624	C	T	HELD_ALL_CC	0,85	1,18	42	57	27	40	60	20
11624	C	T	HELD_MAL_CC	0,85	1,18	13	18	8	18	27	9

AYSNP	ALLEL1	ALLEL2	COMPARISON	RR1	RR2	SIZEA	FREQA	JREQA	SIZEB	FREQB	FREQB
11624	C	T	HELD_FEM_EFF	2,96	0,34	12	22	2	21	30	12
11627	C	T	HELD_ALL_CC	0,78	1,29	45	58	32	40	61	19
11627	C	T	HELD_MAL_CC	0,76	1,32	14	18	10	18	27	9
11627	C	T	HELD_FEM_EFF	3,11	0,32	12	22	2	22	31	13
11644	A	G	HELD_MAL_ADRSULN	0,3	3,32	10	2	18	68	40	96
11650	A	G	HELD_FEM_EFF	0,9	1,11	291	157	425	290	181	399
11654	A	G	HELD_ALL_ADRSULN	1,13	0,89	25	17	33	136	84	188
11654	A	G	HELD_FEM_ADRSULN	1,14	0,88	15	11	19	71	47	95
11654	A	G	HELD_FEM_ADR3ULN	1,09	0,92	32	23	41	71	47	95
11654	A	G	HELD_ALL_ADR3ULN	1,21	0,83	53	39	67	136	84	188
11655	A	C	HELD_ALL_ADRSULN	0,95	1,05	26	35	17	148	203	93
11655	A	C	HELD_FEM_ADRSULN	1,1	0,91	17	23	11	80	104	56
11655	A	C	HELD_FEM_ADR3ULN	0,98	1,02	35	45	25	80	104	56
11656	C	T	HELD_MAL_LIP	0,53	1,87	20	20	20	36	53	19
11656	C	T	HELD_FEM_EFF	2,21	0,45	12	19	5	22	24	20
11656	C	T	HELD_ALL_LIP	0,8	1,25	102	119	85	114	156	72
11825	A	G	HELD_MAL_ADRSULN	0,29	3,4	9	15	3	63	121	5
11914	A	T	HELD_MAL_ADRSULN	0,1	9,58	9	2	16	69	83	55
11914	A	T	HELD_ALL_ADRSULN	0,61	1,64	27	24	30	151	178	124
12008	C	T	HELD_FEM_EFF	0,73	1,37	278	529	27	277	541	13
12008	C	T	HELD_ALL_ADRSULN	null	0	24	48	0	134	256	12
12097	A	G	HELD_ALL_ADRSULN	2,46	0,41	28	6	50	155	11	299
12097	A	G	HELD_FEM_ADR3ULN	1,94	0,51	38	7	69	83	5	161
12097	A	G	HELD_MAL_ADRSULN	3,04	0,33	10	3	17	72	6	138
12097	A	G	HELD_ALL_ADR3ULN	1,7	0,59	63	10	116	155	11	299
12366	A	G	HELD_FEM_UEFF	1,52	0,66	50	82	18	74	104	44
12366	A	G	HELD_ALL_ADRSULN	1,23	0,81	25	40	10	151	229	73

BAVSNP	ALLELE1	ALLELE2	COMPARISON	RR1	RR2	SIZEA	FREQ1A	FREQ2A	SIZEB	FREQ1B	FREQ2B
12619	A	G	HELD_MAL_ADRSULN	0,01	143	10	1	19	71	142	0
12619	A	G	HELD_ALL_ADRSULN	4,53	0,22	27	2	52	151	1	301
13025	A	C	HELD_ALL_ADRSULN	0,81	1,24	28	34	22	151	201	101
13191	A	G	HELD_FEM_LIP	0,72	1,4	83	42	124	79	62	96
13191	A	G	HELD_MAL_CC	1,94	0,52	14	11	17	18	5	31
13191	A	G	HELD_ALL_LIP	0,76	1,31	101	51	151	114	81	147
13937	A	C	HELD_FEM_ADRSULN	0,53	1,89	17	19	15	83	122	44
900002	G	T	CVD_FEM	1,48	0,68	34	23	45	40	15	65
900013	C	G	CVD_FEM	1,24	0,81	35	49	21	40	49	31
900013	C	G	CVD_ALL	1,14	0,88	104	150	58	74	97	51
900025	G	T	CVD_MAL	0,8	1,25	66	41	91	34	31	37
900032	C	T	CVD_FEM	1,68	0,6	25	47	3	37	65	9
900045	C	T	HELD_FEM_EFF	0,42	2,39	12	4	20	22	18	26
900065	A	C	CVD_FEM	1,97	0,51	32	54	10	39	50	28
900065	A	C	CVD_MAL	1,09	0,92	59	80	38	29	36	22
900065	A	C	CVD_ALL	1,24	0,8	91	134	48	68	86	50
900078	A	G	HELD_ALL_ADR3ULN	0,59	1,71	64	116	12	155	297	13
900078	A	G	HELD_ALL_ADR5ULN	0,44	2,27	27	48	6	155	297	13
900078	A	G	HELD_FEM_ADR3ULN	0,51	1,94	38	69	7	83	161	5
900082	A	G	HELD_FEM_ADR3ULN	0,72	1,39	35	25	45	74	70	78
900082	A	G	HELD_FEM_ADR5ULN	0,53	1,88	17	10	24	74	70	78
900096	A	G	CVD_ALL	0,79	1,26	101	157	45	72	125	19
900107	C	T	HELD_MAL_ADRSULN	0,3	3,35	10	2	18	73	43	103
900115	A	G	HELD_MAL_ADRSULN	0,34	2,98	9	6	12	72	91	53
900115	A	G	HELD_FEM_EFF	1,14	0,88	40	58	22	46	62	30
900121	G	T	HELD_MAL_ADR	0,88	1,14	66	47	85	67	56	78
900173	G	T	CVD_ALL	0,64	1,56	23	17	29	22	26	18

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SNP	ALLELE1	ALLELE2	COMPARISON	RR1	RR2	SIZEA	FREQ1A	FREQ2A	SIZEB	FREQ1B	FREQ2B
10000002	A	G	HELD_FEM_EFF	3,35	0,3	12	21	3	22	25	19
10000006	A	G	HELD_FEM_CC	2,77	0,36	31	58	4	22	31	13
10000006	A	G	HELD_ALL_CC	2,34	0,43	44	82	6	38	58	18
10000014	A	C	HELD_ALL_CC	1,69	0,59	45	83	7	39	64	14
10000014	A	C	HELD_FEM_CC	1,68	0,6	31	58	4	22	37	7
10000025	C	T	HELD_MAL_LIP	1,46	0,68	20	29	11	36	43	29